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Table of Contents.

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SOME POINTS IN THE MANAGEMENT OF VARICOSE VEINS.[1]

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VARICOSE VEINS are very common, and the subject is of interest to doctors covering a wide variety of general and special practice. The condition has attracted a great deal of attention over a long period of years. Treatment on the whole has been unsatisfactory, and even today, when the underlying pathology and physics are better understood, there is much controversy on the subject. This has led to a spate of ideas, techniques, terms, tests, and, it must be admitted, some very loose thinking. This lecture is an attempt to deal with some of the more controversial aspects, to simplify these matters, and to present a straightforward approach. The opinions offered are personal, and based on twelve years' work and the operative treatment of over 1000 patients. It is not intended that this lecture shall be an epitome of current literature; no attempt is made to cover the whole subject and much must be omitted.

ANATOMY AND CLINICAL TESTS.

The management of any case depends on accurate diagnosis, and so some remarks on anatomy and on clinical tests are necessary.

Anatomy.

The usual description in anatomical text-books is not much help, nor is it an accurate surgical anatomical picture.

1. The general arrangement of the superficial, deep and communicating veins and the direction of the flow of blood are shown in Figure I. This description is generally accepted and widely known.

2. The long saphenous vein starts at the medial malleolus and runs up the antero-medial aspect of the leg. It is so commonly joined, just below the knee, by a vein running up the postero-medial aspect of the leg that, surgically at any rate, it could be that the long saphenous vein is formed by the junction of these two veins (Figure II). In the upper part of the thigh it is joined by the medial and lateral femoral cutaneous veins and by three named superficial veins—inferior epigastric, circumflex iliac and external pudendal. The arrangement between these veins is subject to the widest variation, and it is further complicated by the fact that the long saphenous vein is sometimes double, the two parts joining before entry into the femoral vein, or each vein having its own set of three tributaries and entering the femoral vein separately. The lateral femoral cutaneous vein is important surgically, for it is often very large, and, running up the anterior aspect of the thigh, takes the place of the upper two-thirds of the long saphenous vein, which under these circumstances is small and unimportant (Figure III).

3. The short saphenous vein runs up the mid-line of the calf from the lateral malleolus, to end, normally, in the popliteal vein (Figure IV). However, it varies a lot in its mode of termination (Figures IV and IVa). It can enter the long saphenous below the knee—a low short saphenous vein—or after crossing in front of the patella—an anterior short saphenous vein. A more common arrangement is for the vein to pass by the popliteal space, running up the outer side of the leg and knee to enter the long saphenous vein about the middle of the thigh, crossing the limb either anteriorly or posteriorly. It is then known

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on December 14, 1950.

as a high anterior or a high posterior short saphenous vein.

4. The communicating veins are a link between the superficial and deep veins, and carry blood to the deep system. They occur most commonly near the knee, at the junction of the middle and lower thirds of the leg, and there is a very constant vein, called the mid-Hunter canal vein, near the junction of the middle and lower thirds of the thigh.

There are other anatomical points, some of which will be mentioned later, but the above are the main points of surgical importance.

Diagnosis.

Diagnosis is not difficult, as varicose veins can be seen at a distance, but such a superficial diagnosis is not enough.

The Arrangement of the Veins.

The general pattern and arrangement of the veins must be ascertained. Attention must be given to the points mentioned in the anatomical description. Inspection of the front and the back of the limb is carried out, and then palpation, which gives more information. The course of the veins can be mapped out accurately in most cases by palpation. The picture obtained by inspection is often incorrect, owing to the tortuosity that is so often present. The short saphenous vein is revealed if the patient bends the knee. If this is not done, even a large short saphenous vein can be overlooked, as towards its termination this vein is beneath the deep fascia of the popliteal space, and this fascia is tense when the knee is extended. A vein in the calf is not the short saphenous vein, unless it can be traced to the popliteal fossa. A common error is to diagnose the postero-medial tributary of the long saphenous vein as the short saphenous vein because its varicosities are in the calf. Another error is to fail to recognize the lateral femoral cutaneous vein towards the front of the thigh and to realize its importance. It often has defective valves and is the cause of the varicosities, while the long saphenous vein may be normal. The type of vein can be ascertained also—that is, a thick, tortuous vein or a true thin-walled varicosity. Both types may be combined in one case. Bunches of varicosities may be connected by straight thick-walled veins (Figure V).

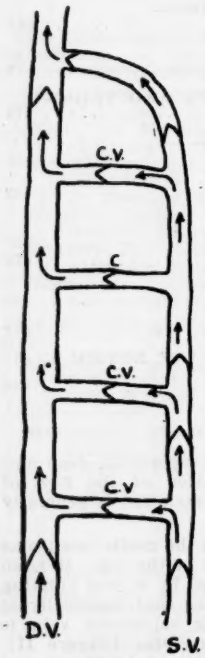

Figure I.

Accurate diagnosis on these lines is essential for treatment, particularly for the correct placing of the incisions.

Special Tests.

Special tests are constantly being devised, and it is well to keep to a few essential tests and drop the rest.

1. The Trendelenburg test is well known and should be carried out first. The test will show the state of the valves at the sapheno-femoral junction and in the long saphenous vein system. If superficial veins in the limb below the tourniquet fill rapidly while it is still in position, a reflux from the deep to the superficial system is proved. It can occur through a communicating vein or through the short saphenous vein if these veins have defective valves.

2. The three-tourniquet test will give more accurate localization of the sites of such a reflux. This test was described previously (Lawes, 1940). It has often been described in the literature and is well known.

3. There now remain the tests for the state of the deep veins. They have diminished in importance in later years, for it is known that the deep veins do recanalize after deep-vein thrombosis. The best test is the reverse Trendelenburg test, which is made as follows. A tourniquet is placed round the upper part of the thigh, with the patient standing. He then lies down and the limb is elevated. The superficial veins will empty if the deep veins are patent. Emptying can be assisted by contracting the muscles—that is, by moving the foot about. No test is entirely reliable, for they all depend on the patency of the communicating veins. The only reliable way to find out the state of the deep veins is by phlebography.

The tests just described are standard tests and give us most of the information we need in planning treatment. There is an important accessory to the Trendelenburg test that should be practised in every case—that is, the estimation of the rate and extent and direction of reflux from above. When the tourniquet is released during the Trendelenburg test it should be noted carefully how quickly the reflux reaches the lower end of the limb, what path it takes, and whether or not a hold-up occurs anywhere in the limb. This is indicated by rapid filling to a point and slow filling below. The importance of the test lies in the fact that the behaviour of the retrograde flowing blood gives an exact preview of what will be the behaviour of a retrograde injection given at the time of the operation. Thus excellent indications are given for the plan of treatment, particularly with regard to the placing of incisions and the size of the retrograde injections.

Figure II.

Two main tributaries forming long saphenous vein. This is a very common arrangement.

Figure III.

Large lateral femoral cutaneous vein and smaller long saphenous vein in the upper part of the thigh.

Treatment.

Operative treatment is necessary for the majority of patients who seek relief, and so this aspect alone will be discussed. Moreover, it is the most controversial aspect.

The main indication for operation is the transmission of pressure from the deep veins to the superficial veins. The aim of the operation is to stop this leak back, wherever it occurs. If this is not done effectively the treatment is a failure, no matter what additional steps are taken. The commonest site for such a leak is at the sapheno-femoral junction. It also occurs at the junction of the short saphenous vein with the popliteal vein, and also through defectively valved communicating veins. This latter condition is referred to as a "blow-out", and though not common it must be sought in every case. If it is not diagnosed and dealt with, treatment will result in failure.

The commonest arrangement is for the sapheno-femoral leak to exist on its own, but it may be combined with either or both of the other types of leak. Similarly, a short saphenous leak or a "blow-out" may exist on its own, but this is not so common.

Extent of Operation.

Section of the long saphenous vein and its tributaries at the *fossa ovalis* is required in the vast majority of cases. This is the basic operation (Lawes, 1946). If a "blow-out" is diagnosed as the sole site of the leak back of pressure, then, theoretically, it is correct to divide this communicating vein and do no more. The same applies to the short saphenous vein. These are the only indications for a low operation—that is, one below the *fossa ovalis*. Division of the long saphenous vein alone anywhere below the *fossa ovalis* is a useless operation. So theoretically the operation consists of stopping the leaks and no more. The results of such treatment have not been satisfactory, and

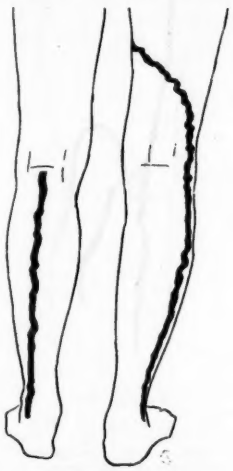

FIGURE IV.

Normal short saphenous vein (left), and high posterior short saphenous vein (right).

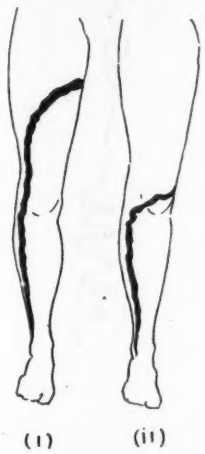

FIGURE IVA.

High anterior short saphenous vein (i) and anterior short saphenous vein (ii).

so more extensive procedures have been done—so much so that it is necessary to retain a sense of proportion in the somewhat bewildering array of techniques, and to strive to get good results by the simplest methods. The method to be described has been used over and over again with good results in all types of cases. The main principles are as follows: (i) the performance of a basic operation, (ii) section of any "blow-out" and of the short saphenous vein if indications are present, (iii) subsidiary section of veins in thigh and leg as necessary for retrograde injection, and as indicated by the pattern of veins and the behaviour of reflux from above.

Some Details of Technique.

1. Section at the *fossa ovalis*. The incision used, all other types having been tried, is one starting over the femoral artery and running medially in the skin crease for one and a half inches and then downwards and slightly medially along the course of the long saphenous vein for a further two to two and a half inches (Figure VI). In a fat person the outer half of the horizontal limb of the incision is replaced by a short vertical limb, the incision being Z-shaped (Figure VI). These incisions are used for certain specific reasons. The crease of the groin is well below Poupart's ligament. As incisions are often described as "so many inches or centimetres below Poupart's ligament", failure to appreciate this fact will result in these incisions being placed too low. The fatter the person, the greater the discrepancy. In any patient an incision below the crease necessitates hard retraction to expose the upper part of the sapheno-femoral junction and to ensure certainty in finding all the tributaries. In a fat person an incision in the crease makes the operation difficult, so the small vertical limb is added in the incision. This gives excellent exposure of the *fossa ovalis* region, does away with the necessity for heavy retraction, and does not offend any surgical principles in crossing the skin crease. The long vertical limb of the incision adds to the safety of the operation. The long saphenous vein can be sought two inches below the *fossa ovalis*, where it is separated from the femoral vein by a thick layer of superficial and deep fascia. Also, at this point, dissection can be carried out below the many tributaries and lymphatic glands found near the *fossa ovalis*. Moreover, the incision allows an extensive examination of the long saphenous vein, which is necessary when the vein is double, is in the form of a loop, or has unusually large or abnormal tributaries. Also the first valve in the long saphenous vein occurs in the top two inches and often catches any instrument that is being passed down the vein. With this incision it is easy to open the vein again below the valve.

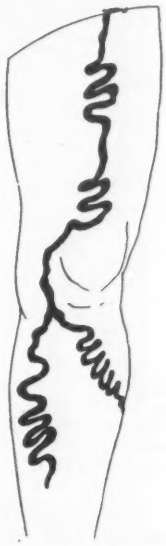

FIGURE V.

Bunches of varicosities connected by straight lengths of vein.

2. Tributaries. All these veins must be divided. This is well known, but they are missed at times, even by surgeons experienced in this work and commonly by the inexperienced. A thorough and careful search must be made, and it must be remembered that anatomical descriptions are apt to be misleading, as variation in the arrangement of the tributaries is great. Some special points are worth mentioning. A tributary often joins the long saphenous vein at the extreme top, being almost a tributary of the femoral vein, usually on the lateral aspect. It will be missed unless a careful search is made high up. It is often quite small at this stage. Another easily missed tributary is one entering the postero-medial side close to the junction with the femoral vein and coming from the rim of the *fossa ovalis* itself. The lateral femoral cutaneous vein should be carefully sought, if clinical examination has suggested that it is enlarged, as previously mentioned.

3. Ligation of the sapheno-femoral junction. The upper ligature must be placed at the sapheno-femoral junction, and this spot must be accurately located and clearly seen. The procedure is comparable with visualizing the junction of the bile ducts in biliary surgery. The femoral vein has been ligated in mistake for the long saphenous vein. The safe identification of the veins depends on the understanding of the method of entry of the saphenous vein into the femoral vein, which is not generally appreciated (Figure VII). It must be noted that the anterior surfaces of the saphenous and femoral veins are in the same plane and that the two veins cannot be identified from this anterior aspect. The junction can be seen clearly from the posterior aspect, and no ligature should be passed until the angle is seen on the posterior aspect of the saphenous vein. The danger lies in clearing the vein too far proximally in an over-enthusiastic search for tributaries. Then a ligature can be passed round the femoral vein above the sapheno-femoral junction. The practice of dividing the saphenous vein an inch or two below the junction and dissecting upwards on its posterior aspect is a bad one and should not be employed. It is easy to snip too far and cut the veins in the region of the junction, where bleeding can be free and difficult to control.

4. Incisions in the knee region. It is often necessary to divide the short saphenous vein in the popliteal space and the long saphenous vein in the region of the knee as well as at the *fossa ovalis*. It is well known and it has been mentioned earlier, that the short saphenous vein at its upper end is beneath the deep fascia. It is not so generally known that the long saphenous vein as it passes the knee also lies deep to a layer of deep fascia. In the superficial fascia there is usually found a small replica of the main long saphenous vein, and failure to appreciate the true state of affairs will result in the main vein's being

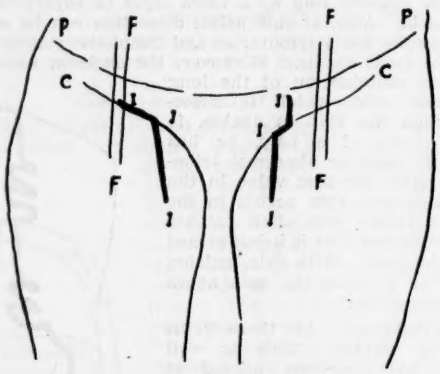

FIGURE VI.

Incisions used in performing section at *fossa ovalis*: P = Poupart's ligament, C = crease in groin, F = femoral artery, I—I—I = incision.

missed. It would seem that the vein is held in position by this fascia in movements of the knee joint. It is also supported by the fascia and the underlying firm structures—a fact of importance that will be mentioned later (Figure VIII).

Obliteration of Veins.

Having sealed the leaks, one can stop and deal with the residual veins by subsequent injection therapy. This can be a tedious business, and in many cases difficult to impossible. There is no doubt that it is wise to continue, at the time of operation, to obliterate as many veins as

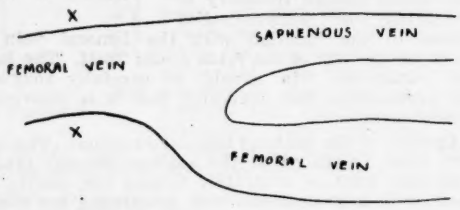

FIGURE VII.

Junction of the long saphenous vein with the femoral vein; "x x" marks spot where the femoral vein can be tied in mistake for the long saphenous vein.

possible. The most satisfactory way of achieving this is by retrograde injection. This is probably the most controversial of all aspects of the treatment of varicose veins. Before an attempt is made to defend and justify treatment by retrograde injection it should be noted that there are other methods of treatment — scrapers, vein strippers, diathermy electrodes *et cetera*—and that they all have their advocates. Such methods are not considered as satisfactory or as universally applicable as retrograde injection. Particularly is this so in severely tortuous and varicose veins, in which a gently flowing retrograde injection will find its own way through the maze where no metal instrument could pass with sureness and safety.

The technique evolved after long experience, and now always used, will be described first, and then will follow a discussion of the objections commonly raised.

Technique of Retrograde Injection.

Before the operation is started the plan of treatment is worked out by careful examination, as already detailed. This consists of (*a*) determining the site of subsidiary sections, if any, and (*b*) deciding on the dose and strength of the sclerosing solution.

A. The simplest arrangement is that in which the long saphenous vein runs, fairly straightly, up the limb and has defective valves. The Trendelenburg test reveals rapid filling of the whole length of the vein. From this it is

FIGURE VIII.

Straight length of long saphenous vein in the knee region.

FIGURE IX.

The meeting of three tributaries in the knee region. Incisions necessary in such a case are shown.

known that a retrograde injection from the upper end of the vein will run down the length of the vein and that no subsidiary section will be necessary. However, recanalization is more likely when long lengths of vein are obliterated. Also it is more difficult to gauge the dose and large injections are necessary. For these reasons it is often advisable to perform a subsidiary section of the vein at the knee.

Subsidiary vein sections are placed so that the retrograde injection given into the exposed vein will obliterate as much of the venous tree as possible. The direction and distance of the flow of the retrograde injection are estimated when the Trendelenburg test is carried out, as already mentioned, and by examination of the pattern of the veins of the limb. Generally speaking, such sections will be necessary in the knee region, where tributaries meet (Figure IX), and below large bunches of varicosities, particularly where smaller straight veins join large varicose bunches (Figure V).

The fascial support of the long saphenous vein at the knee has already been mentioned. It is not uncommon to find that this support prevents much dilatation and varicosity, and that the vein is straight. This tends to cause a hold-up of the retrograde injection at this spot, due to competent valves. It can be predicted by noting the slower filling of the veins in the leg compared with those in the thigh, during the Trendelenburg test. So a second section of vein is made and the retrograde injection is given from the *fossa ovalis* and the knee. (See Figure VIII.)

The commonest site of the junction of tributaries is just below the knee and in the thigh where a high short saphenous vein joins the long saphenous vein. It is

unlikely that the retrograde injection will go down both tributaries in equal and sufficient quantities to sclerose both veins. The vein that will receive the main amount can be predicted, but in order to ensure that both veins will be obliterated, secondary incisions are necessary.

Where large varicose bunches occur it is found that they swallow up so much of the sclerosing material that none reaches the veins below. Also, when smaller veins are found below these bunches, as often happens, they retard the retrograde flow. It is much more satisfactory to use subsidiary incisions.

At the selected points the veins are exposed and opened and the retrograde injection of appropriate dose and strength is given. No force is used in giving the injection. The plunger should move with the greatest of ease; otherwise the injection should be abandoned.

FIGURE X.

Phlebogram after injection of dye into the long saphenous vein from its upper end. The Trendelenburg test showed a reflux down the whole limb. The superficial veins are filled (dense shadow). The deep veins of the leg are also filled (lighter shadow).

B. In general, with regard to the injection, for the whole length of the long saphenous vein 10 to 12 millilitres are a safe dose, and for half the length five or six millilitres. Doses for the injection at secondary incisions will vary according to the length and size of the vein to be sclerosed. Before one gives a dose of 10 to 12 millilitres it is essential to be sure that the material will flow down the whole length of vein easily. To open a vein and to inject hopefully 12 to 20 millilitres of sclerosant, as a routine procedure, is to court disaster.

With regard to the material for injection, one of the "soapy" olamine oleates—for example, "Varistab", "Etalate", "Ethamolin", "Thanomin" — should be used, diluted with sterile distilled water. To make up 20 millilitres, use seven parts of sclerosant and 13 parts of water. For thin-walled veins the solution can be further diluted (six and fourteen parts, or even five and fifteen parts). These are satisfactory but not ideal injections, and in the doses mentioned are safe.

These substances should never be used undiluted in retrograde injections. They are powerful irritants and cause vigorous reactions, both general (with temperatures up to 103° F.) and local (with phlebitis, periphlebitis, cellulitis and great distress to the patient).

With experience the siting of incisions and the estimation of the dose and strength of the injection become more accurate and the results obtained correspondingly better. There is no doubt that satisfactory results can be obtained in all cases of varicose veins, no matter how complicated, by these methods. But a careful history-taking, examination and treatment must be carried out in each individual case. No rule-of-thumb methods suffice.

Discussion of Retrograde Injection.

There has been considerable criticism of the use of retrograde injections in the treatment of varicose veins, particularly in the last few years. This has come about by the increasing number of bad results, many of them tragic. The complications feared are deep vein thrombosis, pulmonary embolism, cellulitis leading to loss of tissue over the veins, gangrene of the limb, sudden collapse of the patient.

The phlebographic studies carried out by Boyd and Robertson (1947) struck a heavy blow at retrograde injections. These workers produced phlebograms which showed that material injected at the groin as a retrograde injection entered the deep veins, the femoral and popliteal, in quantity through the communicating veins; also that material injected at the knee largely remained in the superficial veins. The conclusion from the first group, based on clinical facts, was that no retrograde injection should be given; that from the second, based on phlebographic studies, was that the injection was unsafe from the groin, but much less risky from the knee. These criticisms can be answered, for it is held that the conclusions in both cases are based on unsound reasoning. The problem therefore is approached from two aspects: (i) clinical complications and (ii) phlebographic studies.

FIGURE XIA.

Phlebogram after injection of dye into the upper end of the long saphenous vein. Some of the dye has entered the femoral vein through a communicating vein. Very faint shadow is seen above the point of entrance into the femoral vein as the swift current sweeps dye away.

Clinical Complications.—Sudden collapse, an alarming condition coming on shortly after the injection has been given, must be an allergic phenomenon. It happens occasionally and must be borne in mind. It is less likely to be severe with small doses and weak solutions. It can be guarded against by the giving of a small test dose early in the operation or on the day before.

A violent local reaction may occur. The retrograde injection causes damage to the intima and so clotting in the vein. In some cases extreme reactions have resulted in phlebitis, periphlebitis, cellulitis and local gangrene, all with high temperature, severe pain and disability, and

immobilization of the patient, with added risk of deep vein thrombosis. Some gangrenous processes which have been reported have been so severe that loss of a portion of the limb has resulted. These results are due to incorrect dosage and strength of sclerosing fluid and to incorrect methods of injection. The dangers of injecting large doses of strong solutions have been mentioned. The use of force in giving the injection will drive the material into superficial veins in the skin and cause gangrene. It will also force material into the deep veins, with added risk of deep vein thrombosis.

Cases have been reported of vasospasm of varying degree and severity, leading on occasions to partial loss of the limb. It does not seem to be generally known that the operation of vein ligation and section causes some degree of contraction of the vein, and thrombosis will sometimes occur when no material has been injected. Moreover, some sclerosing substances cause violent spasm. Strong crystalloid solutions—for example, sodium chloride—and organic salts—for example, sodium salicylate—injected into a vein cause violent and agonizing pain from venospasm. This also precludes the use of local anæsthesia, which is essential for early ambulation. The pain passes off usually in a matter of minutes, but spasm in arteries and other veins may be set up. Other strong irritating substances also can cause vasospasm. All these solutions are best avoided, and "soapy" substances should be given in proper dosage and strength. Moreover, at the end of every operation the patient's foot should be examined. If it is found to be cold or blanched, or affected in both ways, treatment should be given at once—the local application of heat, the intravenous injection of "Etamon", lumbar sympathetic block.

FIGURE XIB.

Phlebogram of leg after injection of dye into long saphenous vein at knee. Deep veins are filled and stand out prominently. Superficial veins are also filled.

Complications may be due to faulty operative technique. The errors of technique are: (i) damaging the femoral vein or artery, or both, especially in obtaining hæmostasis; (ii) dividing the wrong vein; (iii) giving the injection into the femoral vein. These errors may seem rather fantastic, but the femoral vein has been divided in mistake for the long saphenous vein. Also, lack of understanding of the previously mentioned mode of termination of the long saphenous vein in the femoral vein can result in the cannula's being placed in the femoral vein. These errors can be avoided by an adequate incision and full dissection of the region.

Phlebographic Studies.—Phlebographic studies concern mainly the complications of deep vein thrombosis and possible subsequent pulmonary embolism. Deep vein thrombosis has been feared for a long time by surgeons using retrograde injection, and this fear is based on the knowledge that the normal flow of blood is from the superficial to the deep veins. It should be remembered that it is a complication rarely seen in spite of all the theoretical reasons why it should occur. It is appropriate at this stage to turn to some of the phlebographic work done on the subject. Boyd and Robertson (1947) presented phlebograms which showed material in the deep vein, particularly after retrograde injection from the groin, and others followed suit. The phlebograms here presented (Figures X, XIA and XIB) were taken in 1944 and were an attempt to find out what happened to injections given in various places—in the *fossa ovalis*, the knee and the ankle. The conclusion reached was that the material injected entered the deep veins in greater concentration from the leg and ankle than from the groin. Another danger that has been mentioned is that material injected stayed in the deep veins for a long time. Phlebograms submitted here show quite the reverse. One (Figure XII) shows that material injected directly into the femoral vein is swept away so fast that no shadow is seen. Another (Figure XIA) shows that material entering the deep vein through a communicating vein in the thigh causes a shadow only at the junction and, being swept away quickly, casts no shadow in the rest of the vein. It might well be asked how two such opposite views could be obtained from phlebography, and also how it is that so few cases of deep vein thrombosis occur if the material injected so readily reached

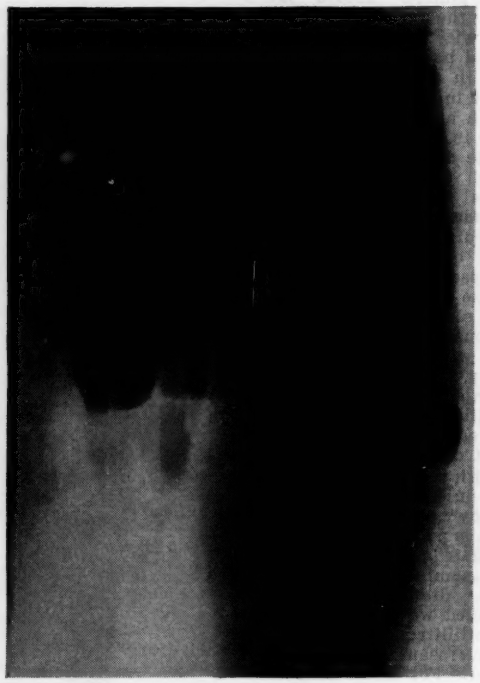

FIGURE XII.

X-ray film taken during injection of 20 millilitres of dye into the femoral vein. No shadow is seen as the dye is swept away too quickly.

the deep veins and remained there. These points will now be discussed.

Phlebography is a tricky art and the greatest care in standardizing the technique is necessary. Small details can upset the interpretation of phlebograms. The commonest error is to regard the behaviour of the radio-opaque material injected as being the same as that of the sclerosing substance. Phlebography is done by injecting large doses of a strongly radio-opaque substance. Retrograde injection of a sclerosant is done by giving the smallest possible dose of the weakest possible solution. Phlebography has confirmed the danger of giving very large doses (15 to 30 millilitres) of sclerosants. Moreover, "soapy" sclerosants, which are used most often, when mixed with blood, immediately form a syrupy compound and so the flow of the sclerosant is slowed down and limited. It is also well known clinically that, in a case

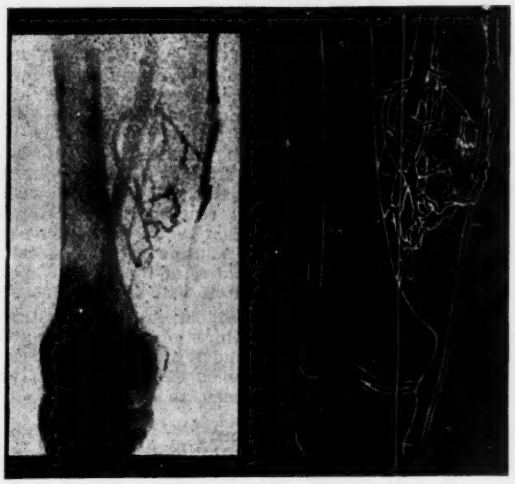

FIGURE XIII.

Phlebogram showing filling of deep veins in thigh due to "hold up" at knee (note very thin vein at knee). Injection of dye from upper end of long saphenous vein. (From *British Medical Journal* of September 20, 1947.)

in which the Trendelenburg test produces a positive result, the sclerosant will sometimes cause thrombosis in the upper two-thirds of the vein—that is, to just below the knee and not lower down. This shows that the material becomes fixed or so diluted that, even if it does reach the lower veins, it has lost its sclerosing power. It will be noted that this refers to cases in which the whole length of the long saphenous vein fills rapidly from above when the Trendelenburg test is performed; thus it is shown that all the blood has run down the superficial vein first and that little, if any, has entered the deep veins until the superficial veins are filled. The fixing of the sclerosant of proper dose would mean that a negligible amount entered the deep system.

An accurately estimated strength of the solution would also be a safeguard, since, if by chance any material did spill into the deep veins, it would by then be further diluted and would be harmless. Large quantities of strongly radio-opaque, non-fixing solution would similarly fill the superficial veins rapidly, but would pass into the deep veins and still be sufficiently radio-opaque to show them in a film. The difference between the two is obvious.

The next important point is the presence of a hold-up in the superficial veins. As has already been mentioned, the most usual spot is at the knee. It is common clinical knowledge that when a retrograde injection is given from the *fossa ovalis* thrombosis often stops at the knee, owing to the hold-up of the sclerosant at this spot. If an injection of 15 to 20 millilitres is given from the *fossa ovalis* a block at the knee will considerably raise the pressure in this part of the long saphenous vein. So the material is forced into other channels. The communicating veins are the largest and they are also natural channels. So excess material passes readily into the deep veins. This, in phlebography, leads to the erroneous conclusion that most of the material enters the deep veins when injected from the *fossa ovalis*. The correct conclusion is that most of the material enters the deep veins when the injection is made from the *fossa ovalis* if a hold-up occurs at the knee.

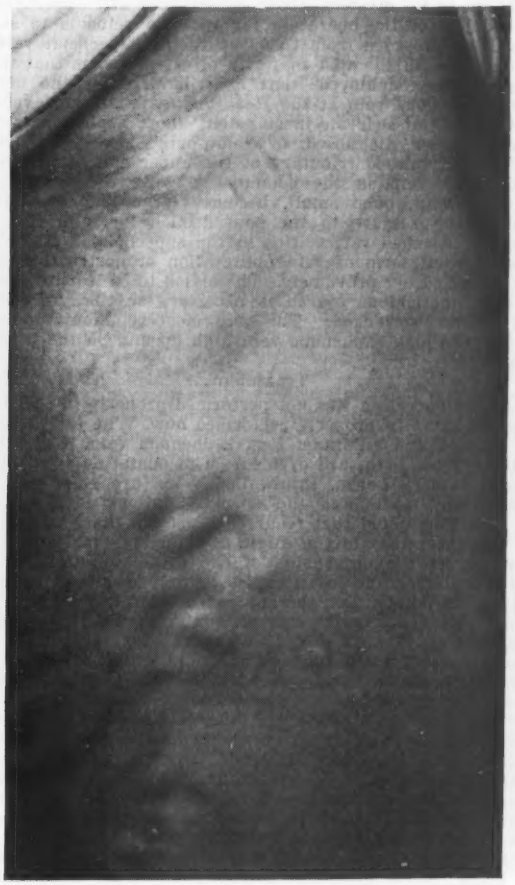

FIGURE XIV.

Recurrence in upper part of thigh to the lateral side of the scar of previous operation. This is a very common finding.

Comment.—Boyd and Robertson's phlebogram shows a large, long saphenous vein in the thigh and a thin, straight vein in the knee region (Figure XIII). This is the typical appearance of a hold-up, and if 15 to 20 millilitres are injected a great deal of it must enter the deep veins. The conclusion reached was that injection from the *fossa ovalis* was dangerous. The correct conclusion should have been that the injection of 15 to 20 millilitres was dangerous. The hold-up at the knee can be diagnosed pre-operatively, and in such a case a small dose (four to six millilitres) of sclerosant should be given. No great rise in pressure in the long saphenous vein will then occur and no massive excess of material will be available for sclerosing the deep veins.

In the leg the same principles hold. The superficial veins will fill first when the valves are defective and only surplus material then enters the deep veins. As in the thigh, no force should be used in giving the injection.

All the evidence points to the fact that danger occurs with retrograde injections when too large a dose or too

strong a solution is used. The solution should be of the minimum strength, sufficient for producing sclerosis. The dose depends on the length of the vein to be thrombosed, and can be estimated by experience. Accurate observation of the reflux and of the presence of hold-up is essential. With these precautions deep vein thrombosis should not occur.

Recurrences.

There is no mystery about recurrences after operation. The object of the operation for varicose veins is to stop any back pressure from the deep to the superficial veins. Recurrence, in the vast majority of cases, means that this has not been achieved—that is, tributaries or the main long saphenous vein at the *fossa ovalis*, or all such veins, have been missed—an incompetent short saphenous vein has not been diagnosed, or "blow-outs" have been overlooked. A missed tributary of the upper end of the long saphenous vein is the commonest cause of recurrence. Such a vein, once small, becomes large and transmits deep vein pressure to the superficial veins, and this is enough to cause varicosities in the superficial system, no matter what form of vein obliteration or destruction has been carried out previously. The lesson to be learnt is that a most meticulous search is necessary so that no tributaries are overlooked. The vein most commonly missed enters the long saphenous vein high up and on the lateral aspect.

Treatment.

As the operation was not performed properly in the first place it must be properly performed now. The *fossa ovalis* is exposed and an intact long saphenous vein, a residual tributary, or both, are divided. The operation is difficult and tedious. Large, thin-walled veins are embedded in dense scar tissue and the normal anatomy is distorted. It should be noted that recurrence usually takes the form, in the upper part of the thigh, of a tortuous mass of varicosities, to the outer side of the original vein (Figure XIV). Retrograde injection is the only means of dealing with this mass. For this to be successful, the injection must be given into the correct vein from the *fossa ovalis*. This is not always easy. When the original operation has been performed through a low incision a two-inch to three-inch stump of long saphenous vein is left. At the second operation the long saphenous vein appears normal at its upper end and it is difficult to tell whether the reflux is through it or through one of the enlarged tributaries. No injection should be given until certainty has been reached. A retrograde injection into a closed stump of vein will produce a vigorous reaction, which may be severe enough to result in local gangrene. Decision can be helped by the following points.

1. A careful pre-operative examination should be made, it being remembered that a vein on the front of the thigh is the lateral femoral cutaneous vein and that the long saphenous vein may dip sharply medially. Also, study of the scar of the previous operation may help.

2. At the operation the new incision can be extended below the original scar, so that the veins can be exposed in their whole length and the true state of affairs can be seen. Usually the divided vein ends in a fibrous cord and there is a leash of veins springing from its end; one of these may be sufficiently large to cause recurrence.

3. Give ten millilitres of distilled water as a trial retrograde injection. If this flows freely down the vein it is safe to give the sclerosant. After the *fossa ovalis* region has been cleared up the remaining veins of the limb must be dealt with by the methods already detailed. The pattern of the veins in recurrence is usually very complex and careful pre-operative examination is necessary to map out their course and place the secondary incisions. If the recurrence has been due to non-treatment of a "blow-out" or to a defectively valved short saphenous vein, this must be remedied. So it is clear that the principle guiding the operative treatment of varicose veins must be followed. The indicated operation must be performed to obtain a satisfactory result. If it is not performed properly the first time it must be the next time. It is quite useless to leave the cause of the recurrence and to perform low sections and local excision *et cetera*.

Apparent recurrence can be caused by the enlargement of normal veins produced by the blood's seeking fresh channels after destruction or obliteration of the main long saphenous system. These veins are never large and are easily treated by injection, provided their appearance is noticed. This can be procured by routine post-operative follow-up or by advice to the patient to return if new veins appear.

Ulcer and Dermatitis.

It is said that varicose veins occur without any ulcer or dermatitis and that an ulcer and dermatitis can occur without varicose veins. These are true statements and are quoted by many as being evidence that there is no connexion between the two conditions. A third fact is overlooked—that is, that in a vast number of cases ulcer and dermatitis heal very quickly and stay healed when the varicose veins are cured.

The Future.

It has been maintained here that operation with retrograde injection offers the best method of treatment for all cases and types of varicose veins (except the milder cases in which injection alone is needed), and that other methods—the use of strippers, scrapers, diathermy electrodes—have limited though good application. This being so, the ideal sclerosing solution must be obtained—one that will cause satisfactory obliteration of the vein with a minimum of local and general reaction. Work for the past eighteen months suggests that such a substance exists and that it is superior to the solution mentioned earlier in this lecture. It is still *sub judice* at the moment, but it is hoped that a statement about it will be possible soon.

Recurrences should be studied carefully and critically. We should be tolerant of the failures of others, hoping that they will be tolerant of ours, and try to find the cause of such failures. The best-intentioned efforts are not always rewarded by the success they seem to deserve.

Summary.

Cure of varicose veins is best attained by: (i) basic operation, (ii) section of "blow-outs" and the short saphenous vein when necessary, (iii) subsidiary sections with retrograde injections given with the precautions that have been detailed.

Recurrences should bring about a careful search for the cause, which is generally a faulty technique.

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THE SYNDROME OF GOUT.

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HIMSWORTH, in the Oliver-Sharpey Lectures to the Royal College of Physicians for 1949, advanced the concept of the "syndrome of *diabetes mellitus*". It is the purpose of the present communication to advance reasons for the application of a similar concept to gout; for, just as the causes of *diabetes mellitus* may be numerous, ranging from acromegaly to obesity, so, I suggest, may be the causes of gout; and just as the secondary effects of hyperglycæmia are manifold, so may be those of hyperuricæmia. For *diabetes mellitus* the one essential is an elevation of the blood sugar level above normal limits; for the syndrome of gout, it is proposed, the one essential is hyperuricæmia.

CAUSES OF HYPERURICÆMIA.

Hereditary Causes.

Gout has long been recognized as hereditary in many cases. It is only comparatively recently, however, that the heredity of hyperuricæmia has been studied (Smyth *et alii*, 1942, 1948; Talbott, 1940; Stecher *et alii*, 1949). On the basis of these studies Stecher *et alii* and Smyth *et alii* (1948) concluded that the gene for hyperuricæmia is a non-sex-linked dominant. It is interesting to note that in 1876 Garrod wrote: "Gout is a constitutional, often inherited, inferiority of the kidneys to excrete the uric acid, an inferiority which does not extend to the excretion of other waste products.

However, hyperuricæmia proved to be much less common amongst the female relatives of gouty patients than it was amongst male relatives (Talbott, 1940; Smyth *et alii*, 1948; Stecher *et alii* (1949). This discrepancy can probably be accounted for, at least in part, by the presence of normally acting endocrine factors. In children plasma urate levels show no sex difference (Wolfson *et alii*, 1949*b*), whereas there is a statistically significant difference between the levels in normal men and normal women (Stecher *et alii*, 1949). The male levels exceed the female levels, the ratio given by Wolfson *et alii* (1949*c*) being 1·0:0·84. Furthermore, after the menopause hyperuricæmia amongst female relatives of gouty subjects seems to be as common as amongst male relatives (Stecher *et alii*, 1949; Smyth *et alii*, 1948; Wolfson *et alii*, 1949*c*).

Thus it may be stated that most cases of hyperuricæmia are hereditary, the gene determining the condition being an autosomal dominant, which by reason of endocrine factors is obscured in women during the child-bearing period. The mode of action of this hereditary abnormality is still not proven, but circumstantial evidence would seem to suggest now that it is on the kidney in diminishing excretion of urates. Talbott, however, declared himself in favour of over-production (Talbott, 1940; Coombs *et alii*, 1940).

Wolfson *et alii* (1949*c*) report a greater clearance of urates relative to urea in females than in males, and it is known that hormones other than sex hormones considerably influence urate excretion. The action of ACTH and cortisone on increasing uric acid excretion and decreasing serum urate levels seems to be upon the kidneys (Benedict *et alii*, 1950*a*, 1950*b*; Bishop *et alii*, 1950).

Acquired Causes.

Hyperuricæmia due to Excessive Production of Uric Acid.

In theory hyperuricæmia may be caused by excess of uric acid of exogenous as well as of endogenous origin. All traditional *régimes* of treatment in gout stressed the importance of limiting purine intake. There is no record of gout arising from ingestion of excess of purines in uncomplicated cases. However, Spence reported two cases of gout in patients with pernicious anæmia who "had eaten a pound of liver a day for three months after the blood cells had been restored to their normal level".

On the other hand, hyperuricæmia resulting from excessive endogenous metabolism is well known. Diseases of the blood may be accompanied by hyperuricæmia of high degree. Lambie states that hyperuricæmia in blood diseases is probably related to the increased nuclear metabolism. It is well known to occur in leuchæmia (Comroe, 1940; Best and Taylor, 1945), and has been demonstrated in pernicious anæmia (Riddle, 1929) and in hæmolytic anæmia (Best and Taylor, 1945). It also occurs with pneumonia, typhoid fever, severe diabetes with acidosis, and congestive cardiac failure (Comroe, 1940).

In association with the various diseases listed above, gout has been reported on numerous occasions with the following conditions: *polycythæmia vera* (Lambie, 1940; Hench, 1947, who thought eight cases of gouty arthritis in 168 of erythræmia was a higher figure than could be accounted for by chance; Davis, 1929; Reifenstein, 1939), pernicious anæmia (Sears, 1933; Spence, 1927), hæmolytic anæmia (Deitrich, 1940; Owen and Roberts, 1937; Meulengracht, 1938), and anæmias of less usual type (Lambie, 1940; Spitz *et alii*, 1949).

It is suggested that sufferers from these diseases in whom gout occurs are predisposed to it by heredity (Lambie, 1940; Collins, 1949), and this is no doubt true in many cases. However, to explain all such cases in this manner seems to invoke a chance association too often to be really convincing. The factor of duration particularly may well be of importance. In this regard recent studies on the amount of uric acid in the body in gout are illuminating. Benedict *et alii* (1949, 1950*a*) and Bishop *et alii* (1950), using isotopic uric acid labelled with N^{15}, have demonstrated a "miscible pool" of uric acid (in immediate physiological equilibrium) from three to twenty-five times as great in gouty as in normal subjects. This largely excludes that contained in tophi. It is possible to think of gout arising only when the limits of the "miscible pool" have been exceeded and tissue deposition begins to occur.

Hyperuricæmia due to Defective Uric Acid Excretion—Renal Disease.

Renal deficiency will, of course, when sufficiently far advanced, cause retention of uric acid and hyperuricæmia, and gout is accompanied by renal disease in a high proportion of cases (22% to 82%—Schnitker and Richter, 1936; Coombs *et alii*, 1940; Kinell and Haden, 1940; Hench *et alii*, 1948). In the present series of 65 cases, 38 are considered to have presented evidence of renal disease on the grounds of either urea retention, consistent albuminuria, or albuminuria with urinary deposit of red cells and casts. The consensus of recently expressed opinion is in favour of the theory that renal disease results from gout rather than causes it (Best and Taylor, 1945; Talbott, 1940, 1949; Coombs *et alii*, 1940; Collins, 1949). Nevertheless, Addis considers that gout secondary to renal disease may occur.

The following case suggests such a sequence. It is not included in the series.

H.E.B., a male patient, aged 50 years, was admitted to hospital on October 6, 1949. He gave a history of pain in the left ankle and left knee for ten days, these joints being swollen and hot. There was no history of previous illness, accident or operation. He was hyperpnœic on his admission to hospital and said that he had been breathless for a week. There was a large amount of albumin in the urine, but the blood pressure was not increased. The patient died a few hours after his admission to hospital. At the post-mortem examination the kidneys were small, pale and contracted, with coarsely granular surfaces. Histological examination revealed chronic nephritis with, in addition, occasional small areas of crystals surrounded by foreign-body reaction.

I feel that an appreciable number of cases of gout may be secondary to nephritic lesions.

SEQUELÆ OF HYPERURICÆMIA.

Deposition of Urates.

What determines the elective sites for deposition of urates is not clear, except in the case of the kidneys. Possibly the profusion of the blood supply in the vicinity of joints is responsible, as stressed by Sir Frederic Wood Jones.

Deposition of urates in the kidney is certainly directly responsible for some gouty renal disease. Calculus formation may be followed by the usual sequelæ of stone, infection *et cetera*, as is exemplified by the following case (Case X of the series).

F.C.B., a male patient, aged sixty years, had suffered from gout for many years. At the age of fifty-seven years he had undergone right nephrectomy for stone. Multiple tophi were present in the vicinity of joints. He died from uræmia. At post-mortem examination the left kidney was found to contain numerous calculi, and multiple abscesses were present. On histological examination little intact renal tissue could be seen.

Hench estimates the incidence of calculus in gouty patients at 13%.

Bell mentioned formation of tophi in the pyramids, and pyelonephritis resulting from obstruction of tubules by urates has recently been reported in a number of cases (Brown and Mallory, 1950; Spitz *et alii*, 1949).

TABLE I.

Case Number.	Name.	Age at Most Recent Attendance. (Years.)	Sex.	Age at Onset of Gout. (Years.)	Highest Blood Uric Acid Level. (Milligrammes *per Centum*.)	Tophi.	X-ray Evidence.	Clinical Description.	Blood Pressure. (Millimetres of Mercury. (Systolic/Diastolic.)	Renal Disease.	Urinary Findings.			
											Albumin.	Erythrocytes.	Casts.	Urea Content. (Milligrammes *per Centum*.)
I	R.G.M.	45	M.	40	6·4	+	−	Frequent attacks of podagra and gouty arthritis in ankles, knees and hands. Tophi in ears.	200/130	+	1/4	+	+	63
II	L.A.F.	33	M.	16	8·5	−	+	Gross deformity of feet with tophaceous ulceration. Deformity in hands and knees.	140/70	+	1/4	Occasional.	Occasional.	101
III	G.C.	14	F.	14	6·6	+	+?	Recurrent arthritis in fingers, wrists, elbows, ankles, knees. Symptomless between attacks. Tophi in hands and feet.	140/100	+	1/12			122
IV	A.P.	57	M.	?	—	+		Death from congestive cardiac failure (for autopsy findings see text). Tophi in hands, elbows, left ear, right knee and kidneys.	180/100	+	1/8			330
V	J.L.	24	M.	24	7·7	−	−	Podagra in left foot. Previous podagra in right foot.	125/85	−		−	−	
VI	V.E.M.	31	M.	29	6·9	+	+	Podagra alternately in each foot and right wrist.	130/90	+	1/4	−	+	53
VII	M.J.	43	F.	? 20	7·3			Recurrent painful swellings in hands and feet "as long as she can remember".	220/130	+	1/4	+	+	41
VIII	R.R.	26	M.	20	10·0	−		Recurrent attacks of painful swelling in wrists, hands, fingers, toes, feet, ankles and knees.	170/120	+	1/6	+	+	84
IX	H.G.B.	65	M.	? 64	7·2	−	−	Onset, attack in knee two days after operation for repair of hernia. Death from cerebral hæmorrhage. (For autopsy findings see text.)	220/140	+	1/4			
X	F.C.B.	60	M.	[1]	15·0	+	−	Gouty arthritis "for many years" (For autopsy findings see text.)	110/80	+	1/2	+	+	226
XI	E.M.H.	33	F.	33	8·5	−		Podagra.	210/120	+	1/12	+	−	188
XII	W.B.	69	M.	49	6·2	+	+	Podagra. Gouty arthritis in hands, and knees. Tophi in hands, feet and left knee.	125/85	−	−	+ ("Few.")	+ ("Few hyaline.")	
XIII	F.W.B.	49	M.	42	4·0	+		Podagra, gouty arthritis in ankles, knees and hands. Tophi in left ear.	170/100	−	−			38
XIV	C.E.M.	31	M.	? 23	15·0	+	+	Arthritis in knees, feet ,elbows and hands. Brief initial attack in 1943; same joints later. (For autopsy findings, see text.)	200/130	+	1/2	+	−	162
XV	A.v.N.	74	M.	[1]	5·3	+	+	Podagra. Tophi in ears.	150/90	−	−	−	−	
XVI	G.P.	37	M.	22	6·8	−		Recurrent podagra. Gouty arthritis in ankles.	140/90	+	1/8			
XVII	W.O.	55	M.	40	3·4	+	−	Frequent podagra. Tophi in feet. Gouty arthritis in ankles and knees.	170/80	+	+			
XVIII	M.O'S.	36	M.	20	6·5	−		Frequent podagra. Gouty arthritis in ankles and knees. Nephrotic syndrome when aged twenty-three years.	140/95	+	+	+	−	39
XIX	P.G.	32	M.	22	6·2	+	+	Podagra. Widespread gouty arthritis with tophi. Admitted to hospital after hæmatemesis.	170/60	+	1/6			215
XX	L.M.M.	32	F.	25	8·0	−	−	Podagra with each pregnancy. Each pregnancy terminated in miscarriage at two or three months.	230/130	+	1/6	+	+	105
XXI	E.D.	62	M.	47	4·0	+		Gouty arthritis in ankles, feet and elbows. Tophaceous ulceration of right second toe—amputation.	150/90	−	−	−	−	26
XXII	C.J.I.	74	M.	34	5·1	+	+	Podagra. Widespread gouty arthritis with tophi in vicinity of joints and in ears. Gross hypertension.	218/116	−	−	+	+	20
XXIII	W.Y.	62	M.	44	4·1	+	+	Widespread gouty arthritis with gross radiological changes. Widespread tophi.	260/140	+	1/6			70
XXIV	G.F.B.	32	M.	32	12·0	−	−	Podagra. Recurrent arthritis in ankles and knees. Nephritis first noticed after petrol burn.	170/110	+	+	+	+	170

[1] No age recorded, "many years ago".

TABLE I.—*Continued.*

Case Number.	Name.	Age at Most Recent Attendance. (Years.)	Sex.	Age at Onset of Gout. (Years.)	Highest Blood Uric Acid Level. (Milligrammes *per Centum.*)	Tophi.	X-ray Evidence.	Clinical Description.	Blood Pressure. (Millimetres of Mercury. Systolic/Diastolic.)	Renal Disease.	Urinary Findings.			
											Albumin.	Erythrocytes.	Casts.	Urea Content. (Milligrammes *per Centum.*)
XXV	M.M.	32	M.	20	6·0	−	+	Podagra ; arthritis in ankles, knees and hands.	130/95	+	+	+	+	54
XXVI	K.D.M.	34	M.	28	8·0	+	+	Podagra ; arthritis in ankles, knees and hands. Amputation of toe because of tophaceous ulceration.	210/140	+	+	+	+	142
XXVII	W.M.	56	M.	36	5·0	+	−	Podagra. Arthritis in ankles, knees and fingers. Tophi in ears.	125/80	−	−	−	−	
XXVIII	H.L.	36	M.	29	6·0	−	−	Podagra. Arthritis in ankles.	144/106	+	+	+	+	
XXIX	F.A.C.	42	M.	41	6·1 (serum 7·6)	−	−	Podagra. Arthritis in wrist.	150/90	−	−	−	−	
XXX	E.E.C.	66	M.	66	5·0	+	−	Podagra on first occasion, six months before death. Further attacks seven and three weeks before death. (For autopsy findings, see text.)	170/105	+	−	−	−	300
XXXI	H.G.	35	M.	35	4·2			Typical podagra.	150/95	−	−	−	−	
XXXII	L.D.	24	M.	24	5·3		−	Podagra. Arthritis in ankle and knee.	135/80	−	−	−	−	
XXXIII	J.B.	50	M.	50	5·2		−	Podagra.	130/80	−	−	−	−	
XXXIV	J.R.	47	M.	47			−	Podagra after operation (herniorrhaphy).	150/100	−	−			
XXXV	C.L.	73	M.	73	3·2		−	Podagra.	150/100	−	−	−	−	
XXXVI	A.T.	81	M.	81			−	Podagra.	220/100	+	1/8	−	−	
XXXVII	S.L.	28	M.	28	5·1		−	Podagra. Death from uræmia, aged twenty-eight years.		+	1/12	−	−	390
XXXVIII	W.H.	62	M.	62	4·3		−	Podagra.	180/80	−	−			
XXXIX	W.E.H.	66	M.	37			−	Podagra. Ankles, wrists and hands also affected.	230/130	+	−			3
XL	W.W.	48	M.	48	4·2		−	Podagra. Onset after minor trauma.	160/100	+	−			35
XLI	S.A.N.	41	M.	39	3·5		+	Typical podagra.		−	Cloud.	Occasional.	−	
XLII	N.H.	50	M.	50			−	Acute arthritis in ankle. Relieved by colchicine.	150/90	−	−	−	−	
XLIII	J.G.	44	M.	42	5·9		−	Acute arthritis in knees. Relieved by colchicine.	140/80	−	Trace.	−	−	
XLIV	L.A.L.	26	M.	24	5·0		+	Typical podagra.	180/130	+	1/2	+	−	50
XLV	J.L.	36	F.	32	4·0		−	Typical podagra.	200/130	+	1/4	−	−	116
XLVI	V.W.	45	F.	[1]		−	+	Typical podagra arthritis in hands and knees.	250/150	+	1/12			
XLVII	A.F.G.	27	M.	25	5·5			Typical podagra. No record of urinary abnormality, but gross hypertension. Papilloedema, hæmorrhage and exudates in fundi.	240/170	+	−	−		143
XLVIII	H.J.B.	39	M.	39	4·3			Typical podagra. Hypertension known for five years.	175/125	+	+			
XLIX	G.H.	62	M.	39	4·5			One attack of podagra, aged thirty-nine years. No further till aged fifty-nine.	130/60	−	+			
L	R.J.C.	26	M.	26				Typical podagra.	120/85	−	−			
LI	E.D.	56	M.	56	3·75			Typical podagra.	140/90	−	−			17
LII	C.F.G.	52	M.	?	4·3			Typical podagra. Widespread gouty arthritis.		−	−			
LIII	J.M.	73	M.	48	5·6			Podagra 25 years ago. Remission till four years ago, when acute arthritis of wrist occurred. Now acute gouty arthritis of wrist and knee.	180/90	−	−			
LIV	J.F.S.	40	M.	40	4·5		−	Typical podagra following *paracentesis tympani.*	160/110	+	Trace.			

[1] No age of onset recorded, but condition present "many years".

TABLE I.—*Continued.*

Case Number.	Name.	Age at Most Recent Attendance. (Years.)	Sex.	Age at Onset of Gout. (Years.)	Highest Blood Uric Acid Level. (Milligrammes *per Centum*.)	Tophi.	X-ray Evidence.	Clinical Description.	Blood Pressure. (Millimetres of Mercury, Systolic/Diastolic.)	Renal Disease.	Urinary Findings.			
											Albumin.	Erythrocytes.	Casts.	Urea Content. (Milligrammes *per Centum*.)
LV	F.G.N.	40	M.	35	5·0			Typical podagra following operation for repair of hernia.	160/100	–	–			
LVI	J.D.	41	M.	35				Gouty arthritis in numerous joints. Alcoholism. Death from carcinoma of mouth. X-ray treatment produced acute attacks of arthritis on several occasions.	160/90	+	+			
LVII	F.A.	22	M.	19	5·4		+	Podagra in both great toes alternately. Recent affection of knees.	140/70	+	Trace.	+	+	
LVIII	C.H.	43	M.	43	3·0			Podagra. Both great toes affected in turn after initial hip pain.	145/95	–				
LIX	L.J.F.	50	M.	43	5·3			Frequent recurrent attacks of podagra. Gout in knees.	120/80	–	–			
LX	J.S.	33	M.	24				Podagra. Fairly frequent recurrent attacks of arthritis in knees and ankles.		–				
LXI	T.S.S.	52	M.	32	5·7	–	–	Frequent attacks of arthritis in feet, knees, ankles and hands.	180/120	+	+	+	+	
LXII	D.M.	30	M.	21	5·3	–	–	Podagra in both great toes; arthritis in elbows, wrists and ankles.	130/80	–	–	–	–	–
LXIII	O.J.B.	36	F.	25	5·0	–	–	Podagra two weeks after birth of third child. Subsequently frequent attacks in both feet and arthritis in left wrist. "Kidney trouble" with first and fourth children at ages of twenty and thirty-one years.	150/110	+	+	+	+	
LXIV	A.N.	48	M.	47	4·0	–	–	Podagra precipitated by Mersalyl given for congestive cardiac failure. Gravel in bladder when aged forty-six years.	170/125	+	+	+	+	71
LXV	W.H.B.	27	M.	25		–		Podagra frequently recurrent; both great toes affected.	150/100	+	+	+	+	

Nephrosclerosis.

Though the factors previously mentioned may account for a certain proportion of nephritic lesions in gout, arteriolar nephrosclerosis is the lesion most consistently recorded (Talbott, 1943; Schnitker and Richter, 1936; Coombs *et alii*, 1940; Brown and Mallory, 1950).

Apart from that of F.C.B., post-mortem examinations were carried out in four other cases in the present series, as follows.

CASE IV.—A.P., a male subject, was aged fifty-seven years. Tophi were present in both hands and elbows, in one ear and in the right knee. Myocardial infarction and multiple pulmonary emboli and infarcts were found. The kidneys weighed three ounces each. The capsule was firmly adherent, the surface was granular. Numerous thin-walled cysts filled with clear fluid were present in both kidneys. There was poor differentiation of cortex from medulla, and pronounced cortical atrophy was present. The arteries were thick-walled and most conspicuous. The renal pelves were normal. Numerous pin-point deposits of urates were found in the pyramids, especially about the tips of the papillæ. The histological diagnosis was nephrosclerosis.

CASE IX.—H.G.B., a male subject, aged sixty-five years, died from cerebral hæmorrhage. Examination of the kidneys revealed deep scarring and pitting on the surface. The capsule stripped easily. The cortex and medulla were not sharply demarcated. The histological diagnosis was nephrosclerosis.

CASE XIV.—C.E.M., a male subject, aged thirty-one years, when examined *post mortem* was found to have tophi in the ears and elbows. The kidneys weighed two ounces and two and a half ounces respectively. Both kidneys were small, with an irregular granular surface exposed after stripping of the rather adherent capsule. A large rather thick-walled cyst about one and a quarter inches in diameter occupied the upper part of the left kidney. A small half-inch cyst lay just below it. Both were filled with clear yellow fluid. The cortex was fibrotic; little cortex and medulla remained. The vessels were not visibly sclerosed. The histological diagnosis was nephrosclerosis.

CASE XXX.—In this case the patient (E.E.C.) had given presumptive evidence of arteriosclerosis in the form of a "stroke" five years before the first recorded attack of gouty arthritis. He had also suffered from *angina pectoris*. Three attacks of acute podagra had occurred six months, seven weeks and three weeks before his death. At the post-mortem examination white chalky deposits were seen under the synovial membranes in the periarticular tissues, and there were deposits of similar material in the bony surfaces of the patella and in the femoral condyles of both knee-joints. These reacted to the murexide test, and microscopic examination revealed typical uric acid crystals. No true tophi were seen. The kidneys were uniformly shrunken with coarsely granular surfaces. Microscopic examination revealed gross arteriolar nephrosclerosis.

Nephrosclerosis is such a ubiquitous lesion that if it is to be considered in a sequential relationship to hyperuricæmia some non-specific action common to it and numerous other factors would have to be invoked. Selye considers nephrosclerosis as one of the renal manifestations of the diseases of adaptation, and instances *diabetes mellitus* as a particular type of stress. Many resemblances can be seen between the "Kimmelstiel-Wilson syndrome" and gouty renal disease, and I suggest that hyperuricæmia acts in this manner.

A further recently recognized piece of evidence may support this idea. Wolfson *et alii* discovered that the

excretion of 17-ketosteroids by gouty patients is very much less than normal. They consider that this can best be accounted for by adrenal secretion of an abnormal androgen. However, as they themselves suggest, a further possibility is that this is a manifestation of chronic stress. Depression of 17-ketosteroid excretion is found in the "resistance phase" of chronic stress (Selye, 1946, 1950). A stress-producing agent of long duration, though not so long as that of hyperuricæmia, is high temperature in the environment, and it has been shown that during the hot Brisbane summer excretion of 17-ketosteroids is diminished (Macfarlane).

Acute Gout.

The prodromata of an acute attack of gout—increased electrolyte excretion (Talbott *et alii*, 1935)—suggest temporary inadequacy of adrenal cortical secretion (Hellman, 1949). The occurrence of gouty arthritis during the few days following administration of ACTH (Hellman, 1949; Robinson *et alii*, 1948), when adrenal cortical function is depressed, suggests that such a temporary deficiency precedes an acute attack of gout. So also does the immediate relief of the acute attack by the administration of ACTH and cortisone (Hellman, 1949; Margolis and Caplan, 1950; Robinson *et alii*, 1948).

It has been suggested that a phasic deficiency of adrenal cortical secretion determines the occurrence of acute attacks of gout (Robinson *et alii*, 1948), and Wolfson *et alii* (1949*c*) consider that temporary 11-oxysteroid deficiency may be related to the abnormal androgen secretion which they previously postulated (Wolfson *et alii*, 1949*a*).

However, although Wolfson *et alii* and Robinson *et alii* presented certain evidence to the contrary, the concept of the gouty patient as in the "stage of resistance" to chronic stress (Selye, 1950) is a tempting one, the stress being constituted either by the hyperuricæmia itself or by its manifestations—arthritis *et cetera*. The precipitation of an attack of acute gout by non-specific trauma of any kind (from X-ray therapy to alcohol consumption) would result from exhaustion of remaining 11-oxysteroid resources as a result of the increased susceptibility of the organism to other stress agents.

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APPENDIX.

The 65 cases listed in Table I have been collected from the records of the Brisbane General Hospital, and in private and consultant practice. The average age of onset of gout in those cases in which the date could be reasonably accurately established was 36·2 years. The youngest patient, a female, was aged fourteen years when the first attack of gout occurred. There were seven females in the series.

In the cases derived from the hospital records (routine admissions), there was no consistency in the care with which family history was sought. No reference is therefore made to family history.

Cases were chosen on the grounds of the typical nature of the attacks, in most podagra being amongst the manifestations, of relief of the acute attack by specific medication (colchicine), of an increased blood uric acid level, or of the presence of deposits of uric acid in tophi or in deeper tissues found at post-mortem examination.

In the first 30 cases there was definite proof of gout—a blood uric acid content greater than 6·0 milligrammes *per centum*, the presence of tophi, or post-mortem evidence. Blood uric acid estimations were made by the method of Folin, and were performed on whole blood. This gives a level lower by a variable amount than that found on serum estimations.

As was mentioned earlier, renal disease was considered to be present in 38 cases on the grounds of urea retention, consistent albuminuria, or albuminuria with urinary deposit of red cells and casts. Hypertension was present in 32 cases (a diastolic blood pressure greater than 100 millimetres of mercury).

HÆMORRHAGIC CONDITIONS CONNECTED WITH THE THROMBOPLASTIN COMPLEX, WITH PARTICULAR REFERENCE TO INHIBITORS.

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IN the last decade it has become increasingly evident that hæmorrhagic diseases characterized by a prolonged coagulation time can be classified into two types. In the one category, as exemplified by true hæmophilia, there is a deficiency of an essential component of the blood clotting system; while in the other group, which clinically simulates hæmophilia, an inhibitor of some step in the chain of reactions which leads to fibrin formation is responsible for hæmorrhages.

The purpose of this paper is to discriminate between these conditions and, in particular, to refer to a type of hæmorrhagic disorder which is characterized by an inhibitor of thromboplastin complex.

Hæmophilia.

The inheritance of hæmophilia is recognized as a recessive sex-linked characteristic, the defect being transmitted by the male through normal daughters to their male children. However, not infrequently no family history of hæmorrhage can be elicited and the diagnosis can be established only by laboratory investigation. Although true hæmophilia in females is theoretically possible and has been observed in female pups following mating of hæmophiliac dogs with bitches heterozygous for the defect (Field *et alii*, 1946; Brinkhous and Graham, 1950), occurrence of this condition in human females has not been established with certainty.

The first pointer to hæmophilia is a delayed whole-blood coagulation time. Sufficient evidence has accumulated to indicate that this test must be rigidly standardized to be reliable. We prefer the technique of Lee and White (1913), in which venous blood is used and the test is carried out in glass or silicone-coated tubes with a measured volume of blood at a standard temperature, usually two millilitres at temperature 37° C.

A delayed coagulation time having been established, further investigation is necessary to determine whether there is a deficiency of an essential factor or whether an inhibitor is present. To detect abnormality in the thromboplastin complex, a useful test is the application of a series of dilute brain extracts prepared from acetone dried brain powder, preferably of human origin. It was necessary to establish the reliability of such a procedure, since it may depend, in addition to the thromboplastic factors, on other coagulation components.

It was observed that K.B. showed at times prothrombin values of 60% to 70% of the normal. Experiments were carried out with blood from normal donors in which the plasma concentration was reduced by dilution with a citrate saline solution. It was found that dilutions between 100% and 60% had little influence on plasma coagulation times when brain extracts from 0·03% to 0·06% were used. It is an advantage to use sodium citrate in the collection of blood in this test because calcium ions are more quickly removed by citrate than by oxalate. One volume of 2·8% sodium citrate solution and nine volumes of venous blood are mixed without delay and the mixture is subjected to centrifugation at 2200 *g.* for fifteen minutes, preferably in a refrigerated centrifuge. It is essential to remove the cellular elements. Although platelets do not influence the plasma coagulation time in concentrations above 0·003% brain extract, a marked influence is observed in lower concentrations (as can be seen in Table I with the use of plasma B). This test was carried out in all cases summarized in Table I.

With regard to cases presented in Table I, it suffices to indicate that the first five patients were males, aged from five to fifteen years, who were examined because of hæmorrhagic episodes. No abnormality in the blood cells could be detected. It could be established that patients Pa. and De. were hæmophiliacs with a positive family history. However, Be. and Sc. are "bleeders" with an apparently normal pedigree, but according to clinical symptoms and results of laboratory tests have to be considered as true hæmophiliacs. Patient St. was diagnosed as having "hæmophilia" by previous consultants, mainly on the evidence that his maternal grandfather told the physician that he was a "bleeder". However, there are no indications of any abnormality in the results of laboratory tests of grandfather or patient St., which exclude them from the group of hæmophiliacs and, as far as could be ascertained, from "bleeders" with a condition due to intravascular causes. It will be observed from the results tabulated that the patients Be., De., Sc. and Pa. showed a definite delay in the plasma coagulation time when tested with brain concentrations in the order of 0·00075%. After blood transfusion the difference disappeared temporarily. The two remaining patients, Mrs. B. and Mr. S., will be discussed later.

Delayed whole-blood coagulation time and deficiency in the thromboplastic complex, as indicated by the tests described, are insufficient for the diagnosis of hæmophilia, because prolonged whole-blood coagulation time can be caused by lack of any one factor of the clotting system, and further similar results could be produced by coagulation inhibitors.

Deficiency of prothrombin and prothrombin accelerator is detected when 3·0% brain concentration is used, and severe fibrinogenopenia can also be excluded in this test.

From the results given in Table I it is apparent that the patients under discussion were normal with regard to these

[1] Working under a full-time grant from the National Health and Medical Research Council.

TABLE I.

Whole Blood and Plasma Coagulation Times of Patients Showing Hæmorrhagic Tendencies.[1]

Method.	Control.	Be.	De.	Sc.	Pa.	St.	Mrs. Ba. (Case I.)	Mr. S. (Case II.)
Whole blood. Lee White (glass tubes)	240–600	2400–3600	720	2000	3600	420	420	3600
Plasma A.[2] Brain extract:								
3·0%	12·5	12·5	12·0	12·5	12·0	12·5	12·0	12·5
0·003%	40	47	42	40	45	40	40	55
0·00075%	90–94	180	150	130	170	85	90	—
0·0003%	102–110	200	180	—	—	—	—	—
Nil	70–170	1200	440	720	1000	175	120	900
Plasma B.[3] Brain extract.								
3·0%	12·5	13·0	12·0	—	—	—	—	—
0·003%	40	45	41	—	—	—	—	—
0·00075%	67	130	115	—	—	—	—	—
0·0003%	—	—	—	—	—	—	—	—
Nil	70–100	480	185	—	—	—	—	—

[1] Figures represent clotting times in seconds.

[2] Plasma A refers to specimens obtained by centrifugation at 2200 *g.* for fifteen minutes.

[3] Plasma B refers to specimens obtained by centrifugation at 200 *g.* for ten minutes.

factors. Coagulation inhibitors of the heparin type are detected by the addition of thrombin or protamine or toluidine blue to plasma. In the case of thrombin it will be delayed, whilst the other two reagents, in suitable concentration, will produce a shortening of the plasma coagulation time if heparin is present. In this series of patients no evidence for the presence of heparin was found. However, coagulation inhibitors of a different nature present in blood and tissues have to be considered. A test which has been found of value to distinguish hæmophilia from hæmorrhagic conditions due to the presence of anticoagulants consists in the recalcification of mixtures of plasma specimens with normal plasma. This test is suggested from observations made by Frank and Hartmann (1927) and also by Patek and Stetson (1936) and by Patek and Taylor (1937), who have found that the addition of small amounts of normal plasma to hæmophiliac blood causes the latter to coagulate in normal time. The test is carried out by preparing mixtures of citrated or oxalated plasma. An amount of 0·1 millilitre of the mixture is kept in a water bath at 37° C. and 0·1 millilitre of M/40 calcium chloride solution is added. Coagulation times obtained in this manner are recorded in the following graph (Figure I).

The curve Be (solid line) indicates results obtained from oxalated plasma of the patient whose other findings are recorded in Table I and is representative of the first four patients mentioned in that table. The results show that addition of 10% of normal plasma to the plasma of these patients brought the delayed coagulation time to a normal level. Further, it will be noted that large volumes of plasma of these patients, when added to normal plasma, will not prolong the coagulation time of the latter. These experiments show that the patients Be., De., Sc. and Pa. lack a plasma component essential for thromboplastin activity and are therefore hæmophiliacs. Curve C represents results obtained by the use of oxalated plasma from normal donors. Dilutions were carried out with 0·85% sodium chloride.

Hæmorrhages Due to Inhibitors of the Thromboplastin Complex.

Finally, Mrs. B. (Case I) and Mr. S. (Case II) will be dealt with.

CASE I.[1]—Mrs. B., aged forty-four years, suffered from a hæmorrhagic disorder which was present over a period of eleven years. In 1936, four months after the birth of her only child, she experienced a severe pain in the left thigh after a minor wrenching. This was the first hæmorrhage, and subsequently over a number of years she had recurrent hæmorrhages manifest usually as hæmatomata, with discoloration of the skin appearing on various parts of the body, usually on trauma but sometimes with no recollection of injury. Treatment given included intravascular injections, which produced large hæmatomata. Her menses, which previously had been normal, became prolonged with excessive loss, including blood clots.

This tendency to bleed gradually became less severe, and during the past three years her menses have been normal and she has had no hæmorrhages. During the bleeding phase routine blood investigations were carried out, but the only abnormality found was a prolongation of coagulation time. In 1936 the coagulation time by the Lee and White method was twenty minutes. Fantl and Nance (1946) investigated the case and found evidence of an antithromboplastin factor. The results of her blood tests are now normal.

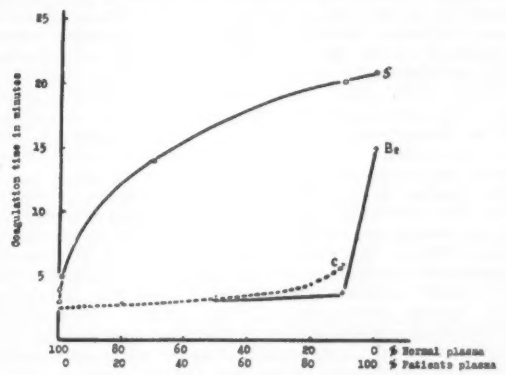

FIGURE I.

She has apparently completely recovered from a severe complaint lasting for eleven years. Her treatment was non-specific, consisting of ascorbic acid and iron tablets. It is not suggested that the treatment was responsible for improvement.

CASE II.—On December 1, 1949, Mr. S., aged seventy-five years, was examined because of a hæmorrhagic condition which had been present for seven months. He had experienced a number of hæmatomata over various parts of the body and also had a persistent epistaxis. Prior to this period, his health had been good and he had never shown a bleeding tendency. The family history revealed nothing of significance. On physical examination of the patient there was pronounced facial pallor and the nostrils

[1] This case was reported in 1936 by Dr. Theo Frank as one of pseudohæmophilia.

contained blood clots. Bruises were present on different parts of the body. No other abnormality was found. The result of a Wassermann test was negative. Blood examination showed a hæmoglobin value of seven grammes per 100 millilitres and a total of 3,000,000 red blood cells, 7000 leucocytes and 300,000 platelets per cubic millimetre; differential count showed 630 band metamyelocytes, 3430 neutrophile cells, 280 eosinophile cells, 2220 lymphocytes and 420 monocytes per cubic millimetre. The skin bleeding time was two minutes. The coagulation time (Lee and White) at 37° C. was thirty-nine minutes (normal, four to ten minutes).

He was given several direct blood transfusions. On one occasion the coagulation time before transfusion was thirty-nine minutes and immediately after transfusion it was twenty-five minutes. Epistaxis continued intermittently, and he had further hæmatomata and a hæmorrhage into the right knee joint. Repeated examinations showed a persistent prolonged blood coagulation time. On December 7 the coagulation time before transfusion was one hundred and ten minutes and immediately after transfusion it was seventy minutes. On May 4 the coagulation time was sixty minutes and the same result was obtained on August 31.

Laboratory tests recorded in Table I indicate a defect in the thromboplastin complex. Since the hæmorrhagic tendency was apparently acquired relatively late in life, true hæmophilia can be ruled out. Except for an apparent thromboplastin deficiency, all the other known factors required for blood coagulation were present in optimal concentration. The result of investigation for an inhibitor of the heparin type was negative. However, the presence of thromboplastin antagonists could be verified on three occasions. The results obtained are given in the form of curve S in the graph.

It can be seen that the addition of less than 0·5% of Mr. S.'s plasma to normal plasma was sufficient to delay coagulation of the latter, indicating the presence of a potent anticoagulant. From this result it would be expected that blood transfusion would be of limited value in repairing the hæmorrhagic condition. Indeed, whole-blood coagulation times were in no instance decreased to a normal level after blood transfusion.

Discussion.

The hæmorrhagic disorders, results of which are presented, are connected with the initial stages of blood coagulation. According to present knowledge, plasma contains in an inactive form the precursor of thromboplastin, termed variously plasma thromboplastin (Howell, 1939), plasmakinen (Laki, 1943), antihæmophilia globulin (Taylor, 1945), prothrombokinin (Lenggenhagger, 1946), thrombocytolysin (Brinkhous, 1947), thromboplastinogen (Quick, 1947). No agreement has been reached on how the activation to thromboplastin occurs. Two theories are still under discussion. According to one theory the precursor becomes activated on certain surfaces or, in other words, we are dealing with a physico-chemical process. A review of the older literature and new experimental evidence for such an assumption have been provided by R. C. Hartmann *et alii* (1949). However, according to another view the platelets are implicated in the activation process. The more recent workers adopting this idea are Brinkhous (1947), Quick (1947) and Milstone (1948). They believe that platelets contain a factor liberated during their disintegration which reacts with the plasma precursor to form active thromboplastin. Whatever the mechanism of this conversion is, experimental evidence supports strongly the view that hæmophilia is a condition due to lack of the plasma-soluble factor required for thromboplastin activity. If we assume this explanation to be correct, the laboratory diagnosis of hæmophilia can be made by the application of the following three tests: (i) Determination of the whole-blood coagulation time. Delay indicates that the hæmorrhagic tendency is due to intravascular causes. (ii) Determination of the plasma coagulation time with a series of brain dilutions. This test will indicate deficiency in the thromboplastin complex. (iii) Determination of the plasma coagulation time with a mixture of patient's and normal plasma. This test will allow the decision whether the condition is due to lack of thromboplastin or is caused by an inhibitor.

Another test which is studied by several workers in this connexion is called the prothrombin consumption test. It is based on an observation made by Brinkhous (1939), who found that the rate of prothrombin conversion in hæmophilic blood was very much slower than in normal blood. However, subsequent workers, Alexander and Landwehr (1949) and Quick (1949*b*) indicate that thrombocytopenia or any condition in which formation or action of thromboplastin is impaired may show an abnormally low prothrombin utilization during and after the clotting process. Therefore it would appear that the prothrombin consumption test will not supply more information that the other tests.

It is essential to establish the diagnosis because of the hereditary implications. Patients Be. and Sc. are considered on the basis of laboratory tests as true hæmophiliacs. However, no family history of bleeding could be traced. No thorough investigation of the pedigree of the patients has been possible, and therefore no discussion of the possibility that we are dealing with the results of mutations is justified. It should be pointed out, however, that it is also the experience of other workers that male "bleeders" with a hæmophilic defect without support from genetic analysis occur not infrequently (Quick, 1949*a*).

With regard to clinical conditions which simulate hæmophilia and which are due to an antagonist of thromboplastin formation or action, several possibilities have to be considered. The inhibitor could act against the conversion of prothromboplastin into thromboplastin, or the formation of thromboplastin could take place and its activity be inhibited.

Several anticoagulants have been isolated from organ extracts. Heparin, the best studied of them, has been shown on occasions to be the causative factor of hæmorrhages. Methods for diagnosis and treatment have been reviewed by Tocantins (1948). The results of tests for heparin in this series of patients were negative. Inhibitors of a different nature connected with certain lipid fractions of blood and tissues have been reported by several authors. Overman and Wright (1948) have isolated from brain, lung or plasma a lipid fraction which inhibited the thromboplastin activity of rabbit lung, and Tocantins *et alii* (1948) have prepared a thermolabile antithromboplastin from human brain and found that in contrast to heparin it has no effect on thrombin. Further, recently Fisch and Towbin (1949) have found that testes contain a clotting inhibitor. Trethewie (1946) has shown that after perfusion of several organs with diluted blood, the perfusate contained an anticoagulant. It is possible that under pathological conditions such inhibitors enter the circulation and are responsible for hæmorrhagic tendencies.

In addition to the anticoagulants mentioned, a third type has been encountered. It has been observed that hæmophiliacs who benefited at first from blood, plasma or plasma products became refractory to subsequent transfusions. The ineffectiveness is considered by Munro and Jones (1943) to be due to the production of antibodies against the antihæmophilic globulin which apparently are also anticoagulants. Several more instances of such inhibitors have been observed, and they are reviewed by Frommeyer *et alii* (1950).

With regard to the two patients, Mrs. B. and Mr. S., it is known that they had acquired the hæmorrhagic condition prior to blood transfusion. Isoimmunization against the antihæmophilic globulin or against the thromboplastin has been considered. However, antibodies reacting with normal plasma components were not detectable in Mr. S.'s plasma. The source of the anticoagulant could not be established.

Excluding hæmophiliacs who developed an anticoagulant after multiple blood transfusions, approximately 10 cases of an acquired hæmorrhagic tendency due to anticoagulants different from heparin have been described previously and are tabulated below (Table II).

From an examination of the histories of the patients in Table II, and from our own cases, it is apparent that no common factor can be shown to be responsible for the appearance of the anticoagulant in the circulation. The experimental data are insufficient to determine the site of

TABLE II.

References to Cases of "Bleeders" Simulating Hæmophilia with Prolonged Blood Coagulation Time Due to a Circulating Anticoagulant.

Males.	Females.
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Dieter, D. G., Spooner, M., and Pohle, F. J. (1949), "Studies on an Undetermined Circulating Anticoagulant. Case Report and Laboratory Findings", *Blood*, Volume IV, page 120.	Hewlett, J. S., and Haden, R. L. (1949), "A Hæmophilia-like Disease in Women", *The Journal of Laboratory and Clinical Medicine*, Volume XXXIV, page 151.
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[1] This case has been reexamined; see Conley, C. L., Ratnoff, O. D., Ellicott, C. E., and Hartmann, R. C. (1950), "Studies on the Initiation of Blood Coagulation. II. An Anticoagulant Inhibiting the Activation of a Plasma Thromboplastic Factor", *The Journal of Clinical Investigation*, Volume XXIX, page 1182.

action of the inhibitor except that it shows affinity to the thromboplastin complex. No specific treatment is available for this condition. It has been observed that plasma or plasma products usually cannot relieve this hæmorrhagic tendency and when given frequently may even aggravate the condition by inducing the formation of antibodies with anticoagulant properties. The suggestion made by Craddock and Lawrence (1947) to use washed red blood cells instead of whole blood should therefore be followed.

Summary.

Hæmophilia is defined as a congenital deficiency disease due to lack of a plasma-soluble precursor of thromboplastin. Laboratory tests to satisfy this definition have been presented.

Frequent occurrence of hæmophilia without family history of bleeding has been observed.

An acquired hæmorrhagic condition, occurring in both sexes, simulating hæmophilia, is described. In contrast to the latter, the condition is due to an inhibitor of the thromboplastin complex.

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PENETRATING INJURIES OF THE RECTUM.[1]

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INJURIES of the rectum result from a multiplicity of causes, and although they may give rise to few signs and symptoms at first, it is imperative that the diagnosis be made immediately and that the gravity of the lesion be realized. Treatment must be instituted forthwith. A mortality rate of 78·5% has been reported in cases with peritoneal involvement (Habhagger, 1912).

Early diagnosis plays a more favourable part in determining the prognosis than the extent of the rectal injury. In other words, a small wound which is overlooked at first is much more likely to be fatal than a more extensive wound which is obvious at once. It is especially in the cases in which an abrasion some distance from the anus is the only visible external lesion that the rectal injury may be overlooked at first. It is to be remembered that the funnel shape of the perineal area may direct a blunt object into the anus without there being any damage to the anus itself. Once the object has entered the anus it is then directed against the anterior wall of the rectum just above the ano-rectal ring. Having penetrated the anterior rectal wall, the object may then pass into the peritoneum, bladder or vagina. In some rectal injuries there may be an upward laceration of the anal canal and rectum; whereas in others, such as accidental perforation at operation, the rectal injury may be very limited.

The prognosis in cases of rectal injury must be guarded, owing to the possibility of complications such as infections, shock, hæmorrhage, injury to other vital structures, fistulæ and incontinence; but these complications should almost be abolished by adequate early operation *plus* chemotherapy.

Penetrating injuries of the rectum are fortunately not common, but during the past two years four such patients have been under my care.

CASE I.—A previously healthy boy, aged nine years, had impaled himself on a piece of iron piping and had divided the anal canal and the lower part of the rectum for a distance of three inches up their right sides. After excision of the damaged tissues a left inguinal colostomy was performed at the Saint George Hospital. Healing of the perineal wound was controlled by packing, so that the new scar tissues would pull the edges of the bowel together. This apparently occurred, for he now has no incontinence and his bowels act normally.

In this case a most satisfactory result was obtained, but it was seven months before the colostomy was closed, and he was discharged from hospital with the perineal wound healed. If primary or delayed suture of the lacerated bowel and anal canal had been performed, infection with fistula, abscess and stricture formation was to be feared, and all that could have been gained for taking this risk was some saving in time.

CASE II.—A male subject, aged seventy-two years, had impaled himself on an unknown object while under the influence of alcohol some eight days prior to reporting for treatment at the Saint George Hospital. During that time his bowels had not acted. On examination, he had an infected sloughing wound extending from the left side of the anus into the anal canal. This wound ended just below the ano-rectal ring, which was not involved. No other rectal injury was detected, and he had no signs or symptoms suggestive of penetration of the peritoneal cavity or of another viscus.

Under general anæsthesia the edges of this wound were widely excised, so that it was converted into a flat area. As there was no evidence of spread of the infection to the pelvic cellular tissues, a colostomy was not considered necessary. The wound was irrigated thrice daily with eusol and a flat dressing soaked in eusol was applied. By the end of four weeks the wound had healed and has given no further trouble. His bowels now function normally.

CASE III.—R.P., aged twenty-five years, a seaman, was admitted to Sydney Hospital on December 30, 1949, with a history of having impaled himself on a stake of wood two hours previously. He stated that the stake had penetrated for a depth of at least three inches, and that it was withdrawn immediately. Since then he had complained of lower abdominal and perineal pain, and there had been some bleeding from the anus. When admitted to hospital he was pale and obviously in pain. His pulse rate was 86 per minute, and his blood pressure was 130 millimetres of mercury, systolic, and 90 millimetres, diastolic. His hæmoglobin value was 14·5 grammes *per centum*. There was diffuse tenderness in the lower part of the abdomen, but there was no guarding of the muscles and no mass was palpable. The perineal laceration extended backwards from the left side of the anus for about two inches and upwards through the anal canal, thus completely dividing the three parts of the external sphincter but not the pubo-rectalis. Three inches from the anus in the anterior rectal wall there was a laceration about an inch in diameter. He was able to pass urine, and this contained only a small amount of blood, detectable on microscopic examination.

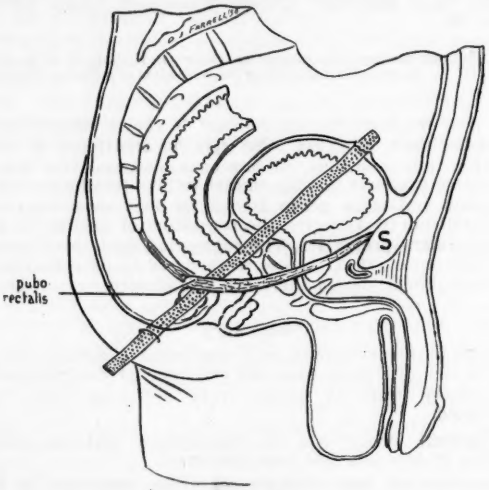

FIGURE I.

The stake of wood (stippled) is shown passing between the pubo-rectalis muscle and the remnants of the external sphincter muscles.

Injections of antitetanic serum (1000 units), gas-gangrene antiserum (10,000 units), penicillin (100,000 units) and streptomycin (0·5 gramme) were given, and a blood transfusion was commenced. Under endotracheal ether anæsthesia administered by Dr. T. Robertson the peritoneal cavity was explored through a lower left oblique incision. An irregular tear half an inch long was present in the peritoneum over the fundus of the bladder, but no injury to the bowel or omentum could be detected. Immediately beneath the peritoneal laceration there was a corresponding wound in the bladder (Figure I). This opening in the bladder was enlarged downwards and backwards to join with a similar but extraperitoneal wound in the middle of the trigone. The edges of the original wounds in the bladder were excised, and then the bladder was repaired with two layers of continuous number 0 plain catgut sutures. A White's tube was inserted into the bladder through the lower end of the abdominal wound. The wound in the anterior rectal wall just above the *levator ani* muscle was not excised or sutured. A loop of the sigmoid colon was brought out through the lateral end of the abdominal wound and fixed in position with a glass rod. The cave of Retzius was drained by a piece of corrugated rubber, and the recto-vesical space was drained by a tube lying between the bladder and its peritoneum. The abdominal wound was closed in layers with catgut for the muscles and peritoneum and with silk for the skin (Figure II). The edges of the perineal wound were widely excised, a flat, shallow wound being left. The external sphincter was not repaired either was the anterior rectal perforation.

[1] Read at a clinical meeting at the Repatriation General Hospital, Concord, on November 2, 1950.

After the operation his condition was satisfactory. The blood transfusion was followed by intravenous infusion of two litres of 4% glucose solution in N/5 saline. Streptomycin (0·5 gramme three times a day) and penicillin (50,000 units every three hours) were exhibited for ten days.

The drains were removed from the cave of Retzius on the second day and from the recto-vesical space on the fourth day. There was very little discharge from or around these tubes.

The bladder was irrigated daily with one in 10,000 "Monacrin" solution, and the White's tube was changed weekly and finally removed on January 31, 1950. No symptoms of urinary infection developed. For the first two weeks the daily excretion of urine averaged 66 ounces. After the suprapubic catheter was removed, urine was passed normally and the wound healed in a few days.

The perineal wound was irrigated daily with eusol and had healed by February 21. Proctoscopic examination then showed that the laceration of the anterior rectal wall was closed. The colostomy spur was crushed, and on March 22

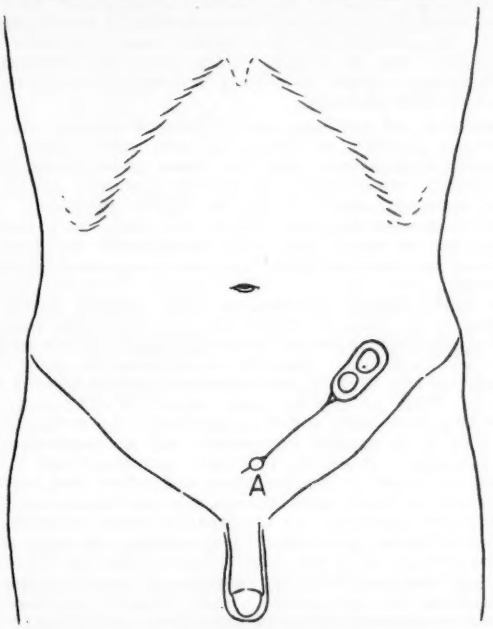

FIGURE II.

Lower left oblique abdominal incision with the colostomy and the suprapubic cystostomy (A).

the colostomy was closed. Four days later his bowels again commenced to act, and on April 7 he was discharged from hospital with the abdominal wound firmly healed, his bowels acting normally without incontinence, and there was no dysuria. Microscopic examination of his urine revealed no cells, casts or organisms.

For the first week after the injury his temperature was slightly elevated (99° to 100° F.) each night, but thereafter it was within normal limits.

CASE IV.—A previously healthy male subject, aged thirty-seven years, was caught between a moving train and the platform, and suffered a crushing injury of the pelvis and extensive lacerations of the perineum and legs. On his admission to Sydney Hospital half an hour after the accident he was extremely shocked and anæmic. His systolic blood pressure was then only 50 millimetres of mercury. The rectum was completely severed from the anal canal, and the posterior portion of the urethra had been avulsed. Antishock measures including blood transfusions and the use of antibiotics were commenced immediately, and after two hours his condition had improved sufficiently to permit the performance of a colostomy and a suprapubic cystostomy under local anæsthesia. These procedures were carried out through a lower left oblique incision. No attempt was made to repair the perineal wound or the structures in it. For the two days after the operation there was some improvement in his general condition, but thereafter it deteriorated and he died on the fifth day after the accident.

In this case the outlook was practically hopeless from the start, because of the cerebral anoxia immediately after the accident and prior to the patient's admission to hospital.

Discussion.

The operative treatment of penetrating injuries of the rectum usually consists of the immediate establishment of a colostomy with spur formation, drainage of the perirectal space by an incision at the side of or below the coccyx, and treatment of injuries of other viscera. It is only in certain circumstances, such as injury at operation, that a direct operative repair of the rectum is indicated at once. Incidentally, the operation at which injury of the rectum most often occurs is probably that of excision of the rectum; but if the laceration is closed immediately, it is then of little importance or consequence.

There has been some controversy in the past as to the place of a colostomy in the treatment of these injuries; but, as it is an additional safeguard in a condition with high mortality and morbidity rates, there would seem little need for further discussion. There is, of course, no place for caecostomy in the treatment of these injuries.

Morgan (1945) advocates injection of one of the insoluble sulphonamides into the distal part of the bowel after the operation, but if there is an unsutured wound of the rectum this can do little good. Penicillin and streptomycin given by regular intramuscular injections, together with injections of antitetanic serum and gas-gangrene antiserum, are, however, indicated in every case.

If there is an injury to the bladder in addition to that of the rectum, repair of the bladder followed by free drainage is essential. Gabriel (1948) advises against a suprapubic cystostomy if a colostomy is also necessary. Even so, it is more difficult to obtain adequate drainage with a urethral catheter, and if a large suprapubic tube is used any bladder infection should not become established. It is possible that a perineal urethrostomy with dependent drainage of the bladder would give results better than either of these methods.

In Cases III and IV no infection of the bladder occurred, even though no "watershed" of strapping between the colostomy and the cystostomy was constructed as advised by Gordon-Watson (1942). In fact it is easier to keep the wound clean when it is not partly covered by strapping. It is interesting to note that there was no more infection of the abdominal wounds than that which usually follows a suprapubic incision alone.

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MULTIPLE MYELOMA: A REVIEW OF THE LITERATURE AND OF EIGHT CASES FROM THE ROYAL MELBOURNE HOSPITAL.

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MULTIPLE MYELOMA is an uncommon disease in which there has been increasing interest recently, both in its clinical diagnosis and in its treatment. Because of the more general use of sternal puncture as a means of diagnosis, there has been controversy regarding its histopathology.

Historical Survey.

The disease was recognized comparatively recently, and was named "*multiples myelom*" in 1873 by von Rustitzky.

Prior to this date the disease as an entity had not been fully appreciated and it was classed with the bone atrophies. Thomas Curling in 1836 wrote as follows:

> There is one species of eccentric atrophy of bone of such rare occurrence that the records of our profession scarcely furnish twenty well-marked examples. Few medical men in the course of a long practice meet with more than one or two instances of the disease in its advanced stage, and many surgeons of experience have never witnessed a case. The disease in question is commonly known as *mollities ossium*.

He then describes a case and lists 16 reported cases, the earliest being in 1700. It is clear from the description that several diseases were included under this title, probably hyperparathyreoidism, Paget's disease of bone, and other conditions, including multiple myeloma.

In 1850 Macintyre reported a case of *mollities ossium*, the first clearly recognizable case of multiple myeloma. He first examined the man, who had a twelve months' history of bone pain, pallor and loss of weight, in October, 1845. Macintyre noted that the urine was opaque and had a specific gravity of 1035 and contained no sugar, and that on the addition of nitric acid the urine cleared, but after an hour a firm coagulum was present. The coagulum underwent complete solution on boiling and consolidation again on cooling. On November 5, therefore, he called in Dr. H. Bence-Jones, who in 1848 reported on the urinary findings in the case. The patient died in January, 1846, and a post-mortem examination was held. The ribs, spine and sternum were "charged with soft, gelatinous substance of blood-red colour, and unctuous feel", and the bones were brittle. Dalrymple in 1846 reported on his examination of portions of the diseased bone, but compared the cytological findings to Birkett's description of the microscopic findings in Solly's case (1844), a case which would now appear due to hyperparathyreoidism.

Although von Rustitzky first named the disease, it was Kahler who, in 1889, first associated Bence-Jones protein with multiple myeloma, and thus the disease gained one of its synonyms of Kahler's disease. J. H. Wright of Baltimore described a case in 1900 in which the tumours were composed of plasma cells. In 1904 Ribbert described an example in which the cells were erythroblasts. Weber and Ledingham in 1909 classified a number of cell types which might be found; they named lymphocytic, myeloblastic, myelocytic, erythroblastic, plasmocytic and mixed forms.

Incidence.

F. R. B. Atkinson in 1937 reviewed 643 cases of the disease, which was the total found in an intensive search of the literature at that time. Regarding the incidence, he noted that of 596 patients 407 were males and 189 females. The age incidence was from childhood to old age, but the vast majority of cases occurred after the age of forty years. However, among 573 cases there were nine between the ages of one and ten years. Race and heredity appeared to take no part in the occurrence of the disease, nor was trauma a precipitating factor. The incidence is variously quoted as between 3% and 25% of all primary bone tumours. The disease is characterized by the occurrence of localized areas of bone destruction by myelomatous tumours. The frequency of the distribution of the lesions as quoted by Willis (1948) is as follows: skull 73%, spine 70%, ribs 68%, pelvis 63%, femur 48%, humerus 43%, and shoulder girdle 40%.

Symptomatology.

The most prominent symptom is bone pain, which because of the multiple nature of the disease may be widespread. Bone swellings, fracture and deformity are common, and at some stage of the disease partial or complete compression of the spinal cord often occurs. Rarely infiltration of peripheral nerves or of the central nervous system may cause symptoms. The renal lesions may occur at an early stage, producing manifestations of renal failure, which are also accentuated when urinary infection follows a cord lesion. Diarrhœa infrequently occurs owing to infiltration of the bowel. The degree of anæmia varies greatly, but it may be of a severe grade early and the patient may present with the debility that results from it. A tendency to hæmorrhage has also been noted sometimes.

Investigations.

The diagnosis cannot usually be made without recourse to special investigations, and those of particular value will now be discussed.

The radiological picture is one of multiple rounded areas of radiotranslucency. The lesions are of various sizes, and may not appear until late in the disease. Some authors consider that the diagnosis may be made in the absence of the characteristic radiological appearance (Bayrd and Heck, 1947).

Examination of the urine frequently reveals albuminuria —in fact, in three-fifths of cases this feature will be present. Slightly less than half the patients will have Bence-Jones proteinuria. There is no constant relationship between albuminuria, Bence-Jones proteinuria and the serum protein level. Because of the renal lesions, casts, red cells and leucocytes may be found in the urine on microscopic examination, and the blood urea level may be elevated and renal function impaired.

Elevation of the total serum protein content, due to increased globulin, is present in most cases. Other biochemical findings are that the serum calcium content is frequently raised, while the serum inorganic phosphate level remains normal or may be slightly increased. The alkaline phosphatase level is often very high. As in several conditions in which there is a considerable proliferation of bone marrow, the blood uric acid level may be above normal.

A hæmatological examination may provide significant findings. In cases in which the serum protein contents are raised, rapid rouleaux formation occurs, which may be seen on blood films. Because of this also the blood sedimentation rate is rapid, and auto-agglutination of cells may occur. There is usually some degree of anæmia at the time of presentation, and it is sometimes of a severe grade. In type it is usually normocytic and normochromic, or hypochromic. However, Lawrence and Rosenthal (1949) found two cases in the literature and report four cases of their own in which polycythæmia preceded the development of multiple myeloma. In the absence of any infection the white cell count is normal or low, neutropenia being sometimes present. In a few cases lymphocytosis may be found, as may eosinophilia. The number of platelets may be diminished in some cases. Less frequent findings are immature myeloid cells and sometimes normoblasts. The only diagnostic feature is the presence of "myeloma" cells in the blood film. These may be atypical cells resembling plasma cells, or may be typical plasma cells. Morrissette and Watkins (1942) found this confirmatory evidence in an appreciable proportion of their cases. In some cases a blood picture suggesting plasma-cell leuchæmia may be found.

The findings on sternal puncture are usually of considerable importance in diagnosis, especially when the radiological picture is doubtful. Normal bone marrow smears contain less than 0·5% of plasma cells. When counts of plasma cells or more atypical myeloma cells exceed 5% or 6% there is good evidence for multiple myeloma. When an actual lesion is aspirated, the majority of the cells will be myeloma cells. Piney described four types of myeloma cells recognizable by sternal biopsy: (i) plasma cells, (ii) myeloblastic cells, (iii) lymphoblastic cells, (iv) erythroblastic cells. From the extensive American literature such authors as Diggs and Surridge (1947) and Bayrd and Heck (1947) found only two types, plasma cells and "myeloma" cells. The plasma-cell type is that in which characteristic plasma cells are found with nuclei with chromatin arranged in clumps, often in a cart-wheel manner, and with basophilic cytoplasm, often with perinuclear pallor. "Myeloma" cells are those which are less typical, the nuclei not showing a characteristic arrangement of chromatin, while the cytoplasm may appear foamy, sometimes with perinuclear pallor and vacuolation, and irregularity of size and shape. Large binuclear cells may be present, some-

TABLE I.

Patient, Age in Years, Sex, Date of Admission to Hospital.	Presenting Symptoms.	Duration of Disease.	Site of Characteristic X-ray Findings.	Bence-Jones Protein.	Blood Findings.	Sternal Puncture.	Biopsy and Post-Mortem Findings.
F.B., 64, M., 9/4/35.	10 months' pain in ribs; 10 months' leg weakness.	10 months.	—	None.	—	—	Plasmocytomata of ribs and vertebræ with compression fractures.
L.McD., 58, F., 19/8/47.	2 months' girdle pains and leg weakness.	2 months.	No characteristic findings.	None.	—	—	Plasmocytomata of ribs and extradural masses of tissue.
P.K., 51, M., 26/3/47.	4 months' shoulder pain, 1·5 months' blood-stained pleural effusion.	4 months.	Ribs, skull, spine, pelvis, femora.	Small amount.	Hæmoglobin value, 83%. Nothing characteristic.	Findings normal.	Myeloid type myeloma in bones as in X-ray films.
H.B., 55, M., 12/10/47.	3 months' back pain, 1·5 months' cardiac failure, 4 days' uræmia.	3 months.	Ribs; other bones not radiologically examined.	None.	Hæmoglobin value, 100%. Nothing characteristic.	—	Plasmocytomata of ribs, vertebræ and pelvis.
C.K., 52, M., 1/6/48.	3·5 years' pain and swelling in ribs, 6 months' pathological fractures of femora.	3·5 years.	Skull, ribs, scapulæ, pelvis and femora.	None.	Hæmoglobin value, 73%. Nothing characteristic.	Findings normal.	Plasmocytomata as in X-ray films, also spine with compression fractures.
H.G., 56, M., 28/6/48.	1 year's malaise, wasting, pallor, hepatosplenomegaly.	1 year.	Ribs, doubtful in skull and pelvis.	None.	Hæmoglobin value, 63%; colour index, 1·23; leucocytes, 11,800 per cubic millimetre; 2% of atypical cells, 0·5% of plasma cells.	—	Reticulosarcoma of vertebræ, pelvis and ribs.
G.C., 64, F., 24/7/48.	4 months' pain in back, 2 months' paraplegia.	4 months.	Spine; other bones not radiologically examined.	Small amount.	—	—	Plasmocytomata of femora and vertebræ.
A.C., 69, F., 5/4/48.	3 years' increasing pallor, brittleness of nails, dyspnœa, 2 months' bleeding from bowel.	3 years.	No characteristic changes till two months before death, when ribs and humerus affected.	None.	1 year before death hæmoglobin value, 34%; colour index, 1·1; leucocytes, 3600 per cubic millimetre; leucopenia with neutropenia; 3 months before death hæmoglobin value 40%, colour index 1·0, leucocytes 3000 per cubic millimetre, 1% of plasma cells.	1 year before death, 12·75% atypical plasma cells; 3 months before death, 56% of plasma cells.	Atypical plasmocytomata of vertebræ, ribs and humerus.

times called mirror-image cells. The cells may contain fine acidophilic granules in their cytoplasm, and after treatment with stilbamidine or antimony compounds, coarse basophilic granules.

Histological section of a biopsy specimen, although not always required, gives confirmatory evidence in diagnosis. As will be discussed later, it also gives the appearance upon which the original classification of cell types was made, as by this method several cell types are recognized. Such authors as Ewing (1940) and Willis (1948) consider that plasmocytoma is the most common, but that the cells may show a number of paths of differentiation, so that immature myeloid and lymphocytic cells may predominate and mixed cell types may occur. The classification of Weber and Ledingham (1909) has been previously mentioned. Atkinson (1937), in his review of 643 cases, was able to list them thus:

Not classified	336
Plasmocytoma	207
Lymphocytoma	16
Myeloblastic	27
Myelocytoma	24
Erythroblastoma	5
Mixed	28
Total	643

Aegerter and Robbins (1947) recently reported a study of 13 cases in which six were of the myeloid type.

Résumé of Case Reports.

The patients whose histories are reviewed were admitted to the Royal Melbourne Hospital over the last fifteen years. Those cases which were selected, eight in number, were those in which histological sections of the lesions were available. The principal features of the clinical manifestations and investigations are set out in Table I. Most of the patients at some stage had had an irregular pyrexia. The blood-stained pleural effusion in one case (that of P.K.) was an interesting association with the rib lesions. In two of the eight cases bone pain was not a presenting symptom. Bence-Jones proteinuria was present in only two of the eight cases. The result of a blood examination and sternal puncture was not always available. The histological sections available were in seven cases from post-mortem examination, and in one from a biopsy of a rib. The full details of the post-mortem findings will not be discussed; they showed the characteristic features of localized tumours replacing bone, there being no new bone formation, but sometimes subperiosteal swelling of the bone. There was infiltration by the tumour cells in other organs such as liver, kidney, spleen and lymph nodes. In the bone marrow not involved by actual tumour there was sometimes an increase in these cells, which may be a matter of a diffuse hyperplasia or perhaps comparable to the infiltration in other organs. In some cases associated conditions were present—for example, bronchopneumonia—and in others dissociated conditions—for example, in one case acute pancreatitis.

The cytological findings in the lesions of bone were of particular interest. Five were typical plasmocytomata. In these the cells presented a fairly uniform appearance in size and shape, and possessed a morphological picture easily recognizable as plasma cells. In one the plasma-cell morphology was less typical, the cytoplasm having a

reticular arrangement. In one the appearance was that of a reticulosarcoma, there being irregularity of cell size and shape, and the cytoplasm having a reticular appearance. Also very large mononucleated cells were present and multinucleated giant cells, the nuclei being centrally situated. In one case the appearance was that of a "myeloid" myeloma (that is, myeloblastoma). The cells were fairly uniform in size, smaller than in the plasma-cell type, with a densely staining nucleus—no nucleoli were seen in the sections—and rather scant basophilic cytoplasm. Fairly numerous polymorphonuclear cells were present. Peroxidase staining of a smear of the lesion from which sections were prepared showed a predominance of peroxidase-positive cells. Other bone-marrow elements were present, including a few plasma cells and also a few normoblasts.

Discussion.

Of the various interesting points arising from a study of the literature a few will be briefly discussed. Blackman *et alii* (1944) investigated the urine and serum of a patient with multiple myeloma of the plasma-cell type (diagnosed by sternal puncture), in whom elevation of the serum protein levels and Bence-Jones proteinuria were present. Using the usual chemical methods and an electrophoretic method, they found there was an increase in β globulin in the serum, and that the abnormal protein in the urine was a β globulin. They stated: "It seems clear that electrophoretic β globulin of serum was excreted in the urine as Bence-Jones protein." From the fact that the molecular weight of Bence-Jones protein is approximately 37,000, while that of serum albumin is 65,000, it is apparent that Bence-Jones protein would be more readily filtered in the glomerulus. But it is not so apparent why it is excreted in some cases in which the globulin level is raised, and not in others. It is interesting to note that the cerebrospinal fluid globulin level may be raised in some cases in the absence of any spinal compression when the serum protein level is elevated. It is considered by several authorities that the myeloma cells themselves produce the abnormal globulin. The Unna-Pappenheim staining method is used by some workers as a measure of protein synthesis occurring in cell cytoplasm, and certainly plasmocytomata stain well thus. However, raised serum globulin levels occur in a variety of diseases, and Bence-Jones proteinuria occurs in myelomata of types other than plasmocytic, and in leuchæmias, secondary carcinomatosis of bone and other conditions.

In general the course of the disease is terminated in a few months only, but it may run on for a few years before death occurs. The cases carrying the better prognosis are those in which lesions are single, for they remain so for some time. Solitary plasmocytoma of bone, with treatment by X rays or excision, may have a good prognosis according to Willis (1948), but most authors agree that it represents the first manifestation of a disease which has a multifocal origin, and that generalized disease will ensue. Solitary plasmocytoma of soft tissue also occurs, usually in the region of the naso-pharynx.

There appears to be a close relation between multiple myeloma and leuchæmia. There are certain parallels to be found in the ætiology of the disease. Thus *polycythæmia vera* may be an event leading up to myeloid leuchæmia, and also may be a precursor of multiple myeloma. Furth, who produced a filterable agent from a fowl which spontaneously developed a type of lymphomatosis (lymphosarcoma), showed that this agent would produce lymphomatosis, myelomatosis and endothelioma in different birds. The agent was comparable in nature to that which will produce transmissible leuchæmia in birds. There seems to be no clear-cut line of demarcation between multiple myeloma and plasma-cell leuchæmia. Thus a patient's peripheral blood may contain numerous plasma cells, and a diagnosis of plasma-cell leuchæmia may well be made until myelomatous bone lesions are discovered. In a similar way in both myeloid and lymphatic leuchæmia bone lesions may occur, the characteristic lesion being chloroma in myeloid leuchæmia.

The feature of special interest derived from the examination of these cases was the variation in cell type found in the histological sections of the lesions. Of the particular cases studied, in only one were atypical cells found in the peripheral blood which might have given a lead to the diagnosis. Of the three cases in which sternal puncture was performed, the marrow gave a diagnostic appearance in one case which was histologically that of an atypical plasmocytoma. In another, in which the lesion was histologically a "myeloid" type of myeloma, two sternal punctures revealed normal findings. But several large series of cases have been reported diagnosed on sternal puncture, both in Europe and in America. Thus, to mention one, Diggs and Surridge investigated 55 cases by this means with conclusive results. They considered that all the cells were either of plasma-cell type or of a more primitive cell type related to plasma cells which they called "myeloma" cells. Many other workers confirm this. But from an examination of the literature, and from the cases studied, there can be no doubt that a number of cell types exist, demonstrable by histological section. It seems possible that the apparent inconsistency reflects in part the very different treatment to which the tissues are subjected in the two types of examination. But the histological examination of sections, upon which the original classifications were built, undoubtedly gives a truer picture of tissue structure.

The classification of Robb Smith (1938), who places the myeloma under the reticulosarcomata, is pleasing in that it embraces the variations in cell type that may be seen on histological examination of sections, for it has been demonstrated that a variety of cell types, from a primitive reticulosarcoma to a number of well-differentiated cell patterns, may be found. It also embraces the apparent interrelationship between the myelomata and the leuchæmias.

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I wish to thank members of the honorary medical staff of the Royal Melbourne Hospital for permission to examine their patients and records.

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SOME OBSERVATIONS ON THE POLIOMYELITIS EPIDEMIC AT STANTHORPE, QUEENSLAND, 1951.

By R. L. GREEN,

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THESE observations made in the last few weeks, though necessarily incomplete, should be of interest to those who have seen the effects of anterior poliomyelitis, and to those who would like to control it.

The Possible Role of Poultry.

The first observation I have to make may have no bearing on the subject, but the coincidence is too great to pass over until proof is available one way or the other.

It has been variously stated that 80% or more of the adult population is immune to anterior poliomyelitis. It is known that the disease can be transmitted to monkeys, cotton rats, white mice and possibly guinea-pigs (for reference see Osler's "Principles and Practice of Medicine"). It is possible that other animals and even birds may act as carriers of the disease.

My attention was drawn to poulty firstly by a relative who had some paralysed fowls, and being a woman, she called on someone else to dispose of these birds. This was just before the outbreak of poliomyelitis here. The local Member of Parliament has in the last week lost two fowls and one duck from paralysis. He points out that in a previous epidemic a similar thing happened to himself and to a friend of his. Some days ago I noticed that some of our fowls had diarrhœa. Yesterday one had paresis of its legs, being able to stand only with great difficulty. Today it appears to have recovered.

As was pointed out above, most people are immune to the disease, so by inference it may be assumed that poultry have a fairly high natural immunity. This would account for this observation's not being very common.

Since some fowls probably contract diarrhœa before the paralysis (as observed in my own fowls), it is natural to assume that if the virus is in the excreta, it would be spread by flies. I have been informed that the virus may be found in the excreta of humans up to twelve weeks after they have recovered from the disease.

It is noteworthy that for the experimental growth of viruses the egg has proved a most satisfactory medium; is it possible that it may convey the virus if not properly cooked?

Parrots and budgerigars can transmit psittacosis, as is well known. Then why should not the domestic fowl also transmit a virus?

Flies and Mosquitoes.

Another observation, which may be pertinent, is that for some months the flies have not appeared healthy or active, and instead of flying away when approached they often have to be literally wiped off.

Mosquitoes usually are not found here, but have probably never been so numerous as at present. This is probably related to the abnormally wet season.

A Combined Case of Tetanus and Poliomyelitis.

The first case in the present series is of interest because of the apparent combination of tetanus with anterior poliomyelitis.

CASE I.—On January 9, 1951, a lad, aged seventeen years, sustained a ten-inch laceration due to a conveyer belt's falling onto his right leg. He did not bother to recieve medical attention, regarding the matter as not serious. On January 23 he reported to me with a history of recent measles and pains in his abdomen for five days. Examination revealed a faint rash and some spots on the inside of his lower lip like Koplik spots. His temperature was 100° F. Next day he had some neck stiffness with arching of his back, which made it difficult for him to sit up. He was given 10,000 units (U.S.A.) of tetanus antiserum and penicillin. Lumbar puncture produced cerebro-spinal fluid containing three to four cells per cubic millimetre, mainly lymphocytes; the chloride and sugar contents were normal; the protein content was 55 milligrammes per 100 millilitres.

At midnight I was called to examine him because he was taking "funny turns". He was unconscious at this stage, with saliva dribbling from his mouth; he also had a stiff jaw and neck retraction; his reflexes were increased, the plantar reflexes being extensor, and his pupils reacted to light. The description of the "funny turns" was vague, except that he went "blue" during them. He was then given 80,000 units (U.S.A.) of tetanus antiserum intravenously and 10,000 units intramuscularly. He immediately had one of his "funny turns", which was a typical tetanus spasm. He went into opisthotonos and became cyanosed. He was given 1,000,000 units of penicillin and promptly had another spasm. With sedation he greatly improved, and he was conscious in the morning, but still had some trismus, with neck stiffness and pain in the abdomen. He was conscious and continued to improve.

On January 27 at 10 a.m. he had no definite paralysis, but had a queer grunting when he breathed. Six hours later he was paralysed almost completely with the exception of his right arm. He gradually became cyanosed, having difficulty in voicing words. At this stage he went into the "iron lung". Next day he felt comfortable, but he had pinpoint pupils suggesting pontine involvement. He later had difficulty with mucus, which was aspirated, and he was given atropine followed by oxygen, but he died at 5 p.m.

Probably the relatively long incubation period of fifteen days accounted for the quick response of the tetanus to serum and the 10,000 units given before the spasms developed no doubt helped. Authorities suggest that fatigue and illness probably increase susceptibility to acute poliomyelitis, and this may be why, since it followed on measles and the spasms of tetanus, the poliomyelitis was so severe.

It is worthy of note that the main cases came from the same locality. One patient who came into hospital two days after this patient was admitted had also to go into the "iron lung".

Some Other Cases.

CASE V.—A boy, aged five years, was feverish for some days and delirious, with a very stiff neck; but the only paralysis he developed was of the face and eye muscles. Apparently he had bulbar involvement only.

CASE VI.—Mrs. N., aged twenty-one years, developed diplopia, which has been troublesome, and also paresis of her left leg.

CASE VII.—The patient was a brother of the patient in Case I. This is best classed as an abortive case.

CASE VIII.—A girl, aged eighteen years, developed a stiff neck followed by headache and loose bowel actions. Although she did not develop paralysis, she apparently acted as the direct vehicle of spread from Case I to Cases IX and XI. In all these the incubation period was eight days.

CASE XI.—A girl, aged one year, was paralysed in both legs on her admission to hospital, but on the following day she developed measles.

It may be of interest to note that some patients appeared to have some involvement of the sympathetic nervous system, in that they required catheterization, and when given enemas retained them, to the consternation of the nursing staff.

Summary.

1. The possibility that poultry may be a means of spreading anterior poliomyelitis has been mentioned. It is noteworthy that most of the patients in this series had some contact with poultry.

2. Poultry, such as chicks or ducklings, should make excellent experimental subjects in place of monkeys.

3. A case of poliomyelitis with tetanus, and another of poliomyelitis with measles, have been described.

4. There is evidence of direct spread of the virus from case to case in subjects with either no immunity or only slight immunity.

5. Cases V and VI approximate closely to encephalomyelitis.

Acknowledgement.

I should like to pay a tribute to the nursing staff of the Stanthorpe Hospital, noting how, in the absence of their matron, who is recovering from an operation, and even when one of their number fell victim, they carried on with a sense of duty and loyalty that one can only admire.

Addendum.

Notes on three other cases of the present series bring the article up to date:

CASE XIX.—Mrs. M. was confined on February 8, 1951. On February 14 she had paralysis of her right thigh. Her baby boy is still breast-fed and shows no sign whatever of the disease.

CASE XX.—This may be a case of indirect spread from Case XIX, but if so the incubation period would not be longer than five days. The patient's mother was a frequent visitor to the patient of Case XIX after her confinement.

CASE XXIII.—A girl, aged two years, was sent in to hospital with a diagnosis of poliomyelitis, which was not confirmed by myself. The day after her admission to hospital she started to vomit a black fluid. She had a mass in her epigastrium, and X-ray examination after a barium enema showed an obstruction of her splenic flexure which looked like an intussusception. This at operation was found to be due to an adherent splenic flexure. The mass was a relatively enormous pancreas, and the greater omentum contained much fat necrosis. Blood-stained fluid was present. The result of Loewi's mydriatic test was positive. Despite drainage she was more toxæmic next day, and died.

Acute pancreatitis has been linked up with mumps, which is a virus disease. Could the virus of poliomyelitis have been responsible in this case?

Reviews.

A LABORATORY MANUAL OF PRACTICAL BIOLOGY.

"PRACTICAL BIOLOGY FOR MEDICAL AND INTERMEDIATE STUDENTS", by C. J. Wallis,[1] is a laboratory manual designed to cover the practical work prescribed for senior school and first year university classes in England. It also covers the work required for corresponding examinations here in Australia. Teachers and students will find this book a valuable addition to their libraries. The experimental work is clearly set out and the illustrations are mostly clear-cut line diagrams. The diagrams have been given as a guide; but not, as the author points out, to be copied by the student into his own practical note-book.

The study of the natural sciences should, in the preliminary stages, train the student to observe and to record accurately. This handbook has this very purpose in view, and those who seek to learn will find "Practical Biology" a useful guide.

The introduction gives general directions for the carrying out of satisfactory work in the laboratory, together with a list of necessary instruments and apparatus.

The main text is divided into four parts. The first part deals with microscopic technique. It will be found to be of great assistance to those who are required to teach the biological sections of general science syllabuses in schools without previous biological training. The young biological student will also find many useful hints. Parts II, III and IV deal with elementary biochemistry, plant biology and animal biology respectively. Probably more experiments are given than the average student will have time to perform. In "Practical Biology" each section is set out in such a simple, clear, systematic manner that it arouses a spirit of inquiry and so trains the student in scientific method and attitude of thought.

The appendices supply much useful information in regard to the preparation of reagents and give suggestions and instructions on general biological technique for the laboratory.

[1] "Practical Biology for Medical and Intermediate Students", by C. J. Wallis, M.A. (Cantab.); Third Edition; 1950. London: William Heinemann (Medical Books), Limited. 8¼" × 5", pp. 420, with some illustrations. Price: 21s.

PROGRESS IN OPHTHALMOLOGY.

AFTER a lapse of seventeen years the fourth edition of "Recent Advances in Ophthalmology" by Sir Stewart Duke-Elder and Allen Goldsmith has appeared.[1] The book is a masterly summary of the more important work which has appeared since the publication of the third edition. It is made up of twelve chapters, each of which is subdivided into sections. At the end of each section is an extensive bibliography which makes the volume of inestimable value to the reader who wishes to probe the subject further. The chapters are headed: "Nature of Intraocular Fluids, Vitreous Body and Blood Aqueous Barrier", "The Circulation of Aqueous Humor, and the Blood Aqueous Barrier in Disease", "Methods of Examination", "Glaucoma", "Bacterial Infections", "Specific Infections", "Virus Diseases", "Chemotherapy and Antibiotics", "Cornea and Conjunctiva", "Cataract", "Endocrine Exophthalmos". In the chapter dealing with methods of examination one finds a description of gonioscopy and biomicroscopy of the fundus, and in the chapter on specific infections a detailed account of brucellosis and toxoplasmosis is to be found. In dealing with cataract and rubella due prominence is given to the work of Australians. The section on endocrine exophthalmos is a good summary of a subject on which the literature is voluminous. The book deserves a place in every ophthalmic surgeon's library.

RADIOLOGICAL PHYSICS.

MANY senior radiologists will remember studying "Physics in Medical Radiology" by Russ, Clark and Watters, which has long been out of print; a second edition has now been largely rewritten by the two first named authors and S. R. Pelc.[2]

In the new edition, the chapters dealing with the fundamental principles of electricity and radiation have been retained with little change, while those on the more modern aspects, such as the measurement of X-ray intensity, the determination of the wave-length of X rays, natural radioactivity, and dosage in radium and radon therapy, have been considerably extended. At this time, however, when important technical advances are being made, the sections on apparatus used in radiography and radiotherapy and on X-ray exposures deserve a much more comprehensive treatment.

Two new sections, dealing with photography and tracer techniques (with the use of radio-isotopes), present a simple account of recent developments in these fields.

An appendix contains the 1948 recommendations of the British X-Ray and Radium Protection Committee. It is unfortunate that the recommendations of the International Commission on X-Ray and Radium Protection adopted in July, 1950, were not available at the time of printing, since many important changes have been made.

The book is well illustrated and excellently printed. It has been written (as is stated in the preface) "to meet the needs of those who seek to keep apace with the developments in medical radiology from the physical and technical aspects", and as such, is more likely to be of use to students in radiology and to other practitioners than to specialist radiologists.

[1] "Recent Advances in Ophthalmology", by Sir Stewart Duke-Elder, K.C.V.O., M.A., D.Sc., LL.D. (St. And.), Ph.D. (London), M.D., F.R.C.S., Hon.D.Sc. (Northwestern), F.R.C.S. (Ed.), F.A.C.S., and Allen J. B. Goldsmith, M.B., B.S. (London), F.R.C.S.; Fourth Edition; 1951. London: J. and A. Churchill, Limited. 8" × 5½", pp. 388, with 139 illustrations, some of which are coloured. Price: 28s.

[2] "Physics in Medical Radiology", by Sidney Russ, C.B.E., D.Sc., F.Inst.P., L. H. Clark, Ph.D., F.Inst.P., and S. R. Pelc, D.Ph.; Second Edition; 1950. London: Chapman and Hall, Limited. 8½" × 5½", pp. 306, with some illustrations. Price: 25s.

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BLOOD CHANGES AFTER GASTRECTOMY FOR ULCER.

In 1929 an important article on the remote results of gastrectomy was published by G. Gordon-Taylor and his collaborators, R. Vaughan Hudson, E. C. Dodds, J. L. Warner and L. E. H. Whitby.[1] In this article it is stated that Deganello in 1900 made the first reference in the literature to a hæmatological examination undertaken after gastrectomy. Since that time many reports of post-gastrectomy anæmia have appeared and the phenomenon has [illegible]thin the experience of most practitioners. (It should be stated perhaps that the article by Gordon-Taylor *et alii* will well repay perusal even at the present time.) Whitby and Britton in their well-known text-book on diseases of the blood point out that the operations of partial gastrectomy, total gastrectomy and gastro-enterostomy are not necessarily followed by a disturbance of hæmopoiesis. At the same time anæmia is common, even though it may be relatively symptomless and discovered only in the course of a routine examination. Whitby and Britton state that anæmia may be produced by total gastrectomy because of the complete removal of the tissue producing hydrochloric acid and the consequent poor absorption of iron. They refer to the work of several authors. Lublin in 1931 found that some patients after gastrectomy had a normal secretion, while others had hyperacidity. A hypochromic microcytic anæmia is the type commonly found—this is reported by Gordon-Taylor *et alii* in the communication already mentioned and by Morley and Roberts. Hurst collected five cases of "pernicious anæmia" after total gastrectomy, and macrocytic anæmia has also been described by Hurst and by Gordon and Japa.

A monograph on blood changes after partial gastrectomy for ulcer has recently been published by Eugen Lyngar,[2] who is chief of the medical department of the Narvik Hospital. The work reported was begun in 1944 at the Drammen Hospital and completed in 1948 at the Trondheim Hospital. Lyngar states that his interest in the type of anæmia that occurs after gastrectomy was aroused because it seemed to be more resistant to therapy than was to be expected. When the anæmia is hypochromic and the patients are achylic, it is natural, he explains, to place them in the group "achylic anæmia". It is generally believed that achylic anæmia is readily cured with iron, but Lyngar realized very soon that this was not unconditionally true of the anæmia of patients who had been operated on, because many of them reacted unsatisfactorily or only very slowly to iron given by mouth. His plan was to study patients who had undergone extensive partial gastrectomy for ulcer only. He excluded patients operated on for cancer because of the possibility that "eventual remissions would influence the blood picture", and patients submitted to gastro-enterostomy because some of them might have intact gastric secretion. Lyngar's investigation covered 146 patients—104 men and 42 women. Most of the patients were in the 40 to 50 and the 50 to 60 year age groups; together these comprised almost two-thirds of the total. There was one patient in the 15 to 20 year age group and there were 17 patients over sixty years of age. There was a control group of 100 patients, 62 men and 38 women; they suffered from gastric or from duodenal or from gastric and duodenal ulcers. The methods of examination included investigation of the peripheral blood and of the sternal marrow, estimation of the serum iron content and of the gastric acidity and the use of clinical, dietary and X-ray data. It should be noted that the diet of the ulcer (control) patients appeared to have been as good as, if not better than, that of healthy persons during the period in which the examination was made, namely during the war. There was found to be little evidence that ulcers in themselves influenced the red blood cell picture. The hæmoglobin percentage was on the average the same as in normal material from about the same war years; the average number of red blood cells was even higher. Volume percentage was practically the same in the normal material and in the ulcer patients, and the mean diameter and mean thickness of the red blood corpuscles agreed well with those found in normal material in peace time. The same was true of the corpuscular volume. In regard to the white blood cells of the controls it is pointed out that deviations from the means have to be very large in order to be considered pathological, and there was little reason to believe that the sternal marrow differed from the normal. The findings on examination of the patients operated on show that these patients have a tendency to anæmia. Basing his conclusions on the hæmoglobin values of the controls, Lyngar finds that 31 patients were classifiable as anæmic at the first examination—16 women and 15 men. In addition two women were found to be anæmic at subsequent control examinations. Thus at least 43% of the women and 15% of the men had become anæmic. When data from case histories were included these figures became 57% and 18%. The anæmia was almost always of a pronounced hypochromic type. There was no indication of "hyperchromia" or other evidence which pointed to the absence of any antipernicious factor. The colour index was low, as also was the iron content of the serum. The total volume of the red blood corpuscles was greatly decreased, much more than their number. On the other

[1] *The British Journal of Surgery*, Volume XVI, 1928-1929, page 641.
[2] *Acta medica Scandinavica*, Supplementum CCXLVII, accompanying Volume CXXXVIII, 1950.

hand the relation between the quantity of hæmoglobin and the total volume was practically always normal. The average diameters of the red blood cells were small, the thickness was similarly reduced in proportion to the normal and to a greater degree than the diameters. There was a pronounced tendency to anisocytosis and microcytosis, but macrocytosis was rare. The sternal marrow findings for the entire group of persons operated on showed that the number of nucleated cells was greater, erythropoiesis was greater and the number of the most immature cell forms was greater in the group operated on than in the control group. The white blood cell picture varied somewhat from that of the control group, but in general there was no evidence that partial gastrectomy as such influenced the picture.

Turning to the results of treatment, we find that Lyngar has some interesting facts to record and arguments to advance. He states that in order to prove that iron deficiency alone is the cause of the anæmia, it is necessary that the blood picture shall become normal in every respect after iron therapy and nothing else. The results of the treatment of 19 patients who could be followed for some time during treatment support the correctness of the iron-deficiency view of causation. The red corpuscles reached a normal count, the colour index rose, the total volume and mean corpuscular volume became normal, the mean diameters of the red blood cells (with one exception) became normal and the thickness of the red cells as well as the volume and saturation indices became normal. The serum iron content did not always reach a normal level and this is thought to be due most likely to the fact that the treatment had not been given for a sufficiently long period. Lyngar's conclusion is that it is highly probable that the anæmia is due to iron deficiency exclusively and can be cured with iron therapy alone. But, as already mentioned, treatment with iron has been stated to be difficult and not always successful. As a matter of fact it was this contention which partly influenced Lyngar to undertake the present investigation. Lyngar admits that the anæmia may be highly intractable and he explains that it is this circumstance which often leads patients to discontinue too soon the taking of iron by mouth and the substitution of other medicines such as liver on the possibility that the anæmia may be of the pernicious type. Lyngar thinks that there is every reason to emphasize the advantages of parenteral therapy in these cases. It is not possible to prove that purely peroral treatment would not have succeeded if continued long enough. At the same time it has been found sometimes that the patient reacts more readily to parenteral than to peroral therapy and occasionally it appears that no effect is obtained until the patient has received some iron parenterally. This question is all bound up with the resorption of iron from the intestinal tract. On this Lyngar writes at some length. He refers *inter alia* to a possibility dependent on a theory advanced by Granick in 1946, that the mucosa cells take up iron from the intestinal tract, but do not release it again to the serum until they are themselves saturated with "ferritin". The cells of the mucosa might have their functional capacity reduced as a result of iron deficiency and this functional capacity would be improved more rapidly by parenteral than by peroral therapy. It is not possible to control Granick's theory experimentally, but Lyngar quotes in support interesting figures showing by intravenous tolerance tests the rate of disappearance of iron from the blood after parenteral injection.

The subject on which Lyngar has written his monograph is of absorbing interest; he has done a service in discussing it and his observations are of great value. But much remains to be learned about the subject. The removal of gastric tissue must be looked on as the cause, but we need to remember that all patients operated on by gastrectomy do not become anæmic. The anæmia, it is true, does develop slowly, but a large percentage of Lyngar's patients escaped. It is possible that at a later date some of these might have manifested signs of anæmia. Lyngar shows that the onset of anæmia bears some kind of relationship to the normal loss of iron by the body. This means that after operation there is some interference with the supply of iron to the body—the resorption of iron is delayed or checked. As Lyngar expresses it, there may not be pathological loss of iron. It means that if the loss of iron is not equalled by its resorption, anæmia will result. This is true in regard to persons who have not been deprived of their stomachs. What needs to be learned is what removal of stomach tissue really does to the organism. The alimentary function is complex and is related to endocrine, vascular and other functions of the body, the whole working as an intercoordinating and interdependent system or systems. When we remove one of the units of the system the loss has to be made good and there is small wonder that in certain cases breakdown occurs. Really the lesson to be learned is that gastric resection is an unphysiological procedure—it is a mutilation carried out in hope of subsequent adjustment of disordered harmonies. No patient can be said to be cured of his ulcer by gastrectomy in the sense of being made whole, even if he has no subsequent gastric symptoms and is free of anæmia. Until we have more knowledge the mutilation will probably have to find its occasional use.

Current Comment.

STRANGE GUESTS IN THE FEAST.

THE human stomach becomes the repository for a remarkable variety of substances and objects that have no legitimate business there. A good deal that is of doubtful respectability makes its entry under the guise of food and drug therapy; its true identity unsuspected, it slips in amongst the invited guests of good repute. Other items, though certainly invited guests, bear such a strange character that their invitation is to be wondered at. Recent Press reports from London are by no means incredible in their story of a labourer, suspected of having peritonitis, who was found at operation to have in his abdomen a bicycle wrench, a large bicycle bolt, part of a bicycle axle, a steel twist drill and a coiled spring. The patient is reported to have said that he had swallowed the articles and also a piece of hacksaw, which was recovered later. This is, of course, an outstanding collection of strange guests in the feast ("in the feast" appears more appropriate to the metaphor than "at the feast"), but it will be readily matched in quality, if not always in quantity, by reference to the records of practically any children's hospital, mental institution or gaol infirmary. Of greater clinical and pathological interest than collections of aberrant ironmongery (much as these may delight the psychiatrist and test the surgeon) are

the strange objects known from antiquity as "bezoars". These concretions of hair or other material found in the stomachs of animals and men were regarded as having medicinal properties, and their name is thought to be derived through the French and Arabic from a Persian word meaning antidote or counterpoison. According to R. L. Tondreau and B. R. Kirklin,[1] these concretions, which were only described as occurring in animals up till the eighteenth century, were worn as charms or were taken internally for the prevention or treatment of various afflictions, including the bites of poisonous reptiles, the plague, leprosy and epilepsy. Even within the past half-century, certain bezoars known as "madstones" were available in a few localities for application to the bites of supposedly rabid dogs. As recently as 1929 the following advertisement appeared in a Missouri newspaper: "For Sale, Madstone large enough for two."

The first recorded case of bezoar in man seems to have been reported in 1779, but most of the total, which now stands at about 400, have been reported much more recently. The earliest recorded cases were trichobezoars (hairballs), and this is still the most common type, though slightly on the decrease. Hairballs occur mostly in women, but occasionally in men. They are composed of hair of various lengths, firmly matted together and sometimes filling the stomach. The hair is usually that of the person concerned, but it may be that of another person, or of a horse, cow or goat; cotton and wool thread, string and bristles have been found mixed in it, as well as particles of food. Most patients with trichobezoars appear to be mentally normal, and explanation for their trichobezoars is difficult; some neurological or psychiatric disturbance is usually assumed, but it is not proved. It was thought that in the era of long hair the biting and swallowing of hair was easy, and therefore more likely to be indulged in, but the relatively small decrease in incidence since short hair has been fashionable indicates that length of hair is not a major factor. Hairballs are produced gradually and cumulatively. Why they are not got rid of more often as the hair forms balls is not understood. The next bezoar in order of frequency is the phytobezoar, which is made up of the stems, fibres, leaves, roots and seeds of fruit and vegetables, moulded into compact masses with intermingled debris. Nearly all are persimmon bezoars, and most of these have been reported from Japan and from the "persimmon belt" of the United States. Their formation is not gradual but immediate, and results from the eating of a large quantity of persimmons at one time, particularly when the stomach has been empty; suitable subjects mentioned by Tondreau and Kirklin are famished hunters, golfers and other men engaged in outdoor pursuits. The most reasonable explanation for persimmon bezoars has come from Japan. According to this, the pulp of persimmons contains an element, shibuol, which is precipitated by dilute solutions of mineral acids. Gastric juice is sufficiently acid to cause this precipitation, with the resultant production of a sticky mass. Various other vegetable components have been found in phytobezoars, but the total number of these is few and most of the vegetable substances concerned are represented only in single cases. Other substances making up bezoars have included asphalt, bismuth carbonate, magnesium and sodium carbonate, paraffin, salol and shellac, the last being the most common of the group. Shellac is soluble in alcohol and insoluble in water, hydrochloric acid and alkaline solutions. It is used by painters and furniture workers, among whom most of the 11 recorded cases of shellac bezoar have occurred. They apparently may ingest some of it in solution; then absorption of the alcohol and dilution of the solution with water lead to precipitation of the shellac and formation of concretions. Tondreau and Kirklin state that the symptoms and signs of bezoars are so often indistinguishable from those of many other abdominal affections that the diagnosis usually is not suspected clinically. The diagnosis may be made at operation or *post mortem*. However, radiological manifestations are, as a rule, pronounced and characteristic; the usual diagnostic appearance is that of a normal gastric outline with a central radiolucent reticulated or mottled area which corresponds to a mass that often is movable. The most frequent complications are gastro-duodenal ulceration and intestinal obstruction. The treatment is surgical removal. Prophylaxis is not perhaps of great importance in view of the rarity of bezoars. It may be difficult for trichobezoars, in view of the obscurity of their essential cause; it is fairly obvious for other forms of bezoar, and is well summed up in the last words (according to Mr. Hilaire Belloc) of Henry King, "who chewed bits of String, and was early cut off in Dreadful Agonies".

> . . . "Oh, my friends, be warned by me,
> That Breakfast, Dinner, Lunch, and Tea
> Are all the Human Frame requires . . ."
> With that, the Wretched Child expires.

It is well to be discriminating in one's guests at and in any feast.

[1] *Surgical Clinics of North America*, August, 1950.

SONNE DYSENTERY RESISTANT TO SULPHONAMIDES.

AN outbreak of dysentery in hospitals, and particularly in a children's hospital, is a not unfamiliar event, but it is usually expected to be controlled by drugs of the sulphonamide type. Merlin L. Cooper and Helen M. Keller describe a small but acute outbreak of dysentery of the Sonne type which was not fully controlled by sulphadiazine.[1] The children affected were only five in number, but were in different cubicles of a series of small wards holding 28 children in all, and the disease appeared within ten days. The illness was acute, with fever and toxic symptoms. Cultures of the stools revealed the *Shigella sonnei* in each instance, and each child was promptly isolated as soon as the bacteriological diagnosis was known. The acute phase of the illness soon passed, suggesting that the exhibition of sulphadiazine had controlled the infection, but repeat cultures showed that the organism was still present in the stools. One patient, however, who was also suffering from glomerulonephritis and was treated with chloramphenicol instead of sulphadiazine, was well after two days' treatment, and the stools no longer contained demonstrable organisms of the dysentery type. One of the other patients had a relapse which was clinically controlled by sulphadiazine. Previous experience with the Sonne infections had shown that the organism disappeared from the stools promptly, and therefore it was suspected that the strain in question might be resistant to the drug, especially as the organism persisted in cultures even after twelve days. Accordingly, chloramphenicol was given, in doses of 125 to 250 milligrammes every four hours, diminishing to three times daily. The administration continued for ten to twelve days. There were no toxic symptoms, and the *Shigella sonnei* rapidly disappeared from the stool. It is interesting to note that the same success was gained in the treatment of a carrier responsible for the outbreak. The distribution of the infection aroused suspicion, and inquiry showed that a nurses' helper in the ward had been off duty for three days with mild diarrhœa three months previously. She was investigated in hospital, and was found to be still carrying the *Shigella sonnei*. Follow-up cultures showed that this carrier was rendered innocuous and remained so several weeks afterwards. Further investigation of the patients was made to determine the blood levels of chloramphenicol, and also the presence of agglutinins for the individual strains of the organism. It appeared that the administration of the antibiotic did not inhibit antibody formation. Experiments were then carried out to determine if inhibition of the organism by the drugs could be proved in cultures.

Other workers have previously shown that chloramphenicol has a bacteriostatic action on the *Shigella sonnei*, though it does not appear to have been used for the clinical disease. In the present series the authors

[1] *American Journal of Diseases of Children*, December, 1950.

found that each strain of the organism was highly resistant to sulphadiazine, as evidenced by in-vitro sensitivity tests, but was quite susceptible to chloramphenicol and three other antibiotics. Therapeutic tests in white mice also showed that the animals recovered from experimental infection if the antibiotic was given, but were not protected when sulphadiazine was given. The authors do not appear to have tried the effect of the slightly soluble sulphonamides, which one might think would be more likely to prove effective in preventing a carrier state from developing. This is another instance of the phenomenon of non-sensitivity appearing as an apparently intrinsic character of bacteria, and shows how epidemics might not only arise, but persist even in spite of what appeared to be satisfactory treatment.

CORTISONE IN ACUTE GLOMERULONEPHRITIS.

Now that cortisone and the adrenocorticotropic hormone are becoming more generally available for clinical use, there is evidence that these substances are being subjected to clinical trial in a wide field. The coincident interest in the concept of the stress syndrome has probably stimulated the spirit of inquiry also, and in addition, when the doctor sets sail on seas as yet little charted, he likes to provide himself with new equipment. Charles H. Burnett and a team of colleagues report from the Boston University School of Medicine the results obtained from cortisone in the treatment of a patient with acute glomerulitis.[1] This trial was, of course, suggested by the success of the hormone in acute rheumatic fever. The patient was under observation for forty-three days, and received 200 milligrammes of cortisone daily for twelve days. He was a boy, aged fifteen years, who had been ill four weeks previously with a sharp indisposition lasting five days in which he had fever and coryza preluded by a rigor. During the next week the urine was rusty coloured, and a diagnosis of acute nephritis was made. Investigation showed an absence of fever, heavy proteinuria, with leucocytes and erythrocytes in the urine, and occasional casts. The sedimentation rate was increased. The blood non-protein nitrogen content was 67 milligrammes and the total protein content was 8·4 grammes per 100 millilitres. A diet of 3132 Calories was given, with 95 grammes of protein. The renal condition was thoroughly investigated for five days before the cortisone was given, and for eleven days after the treatment ended. The full details of the daily microscopic and biochemical investigations are given in the article, and may be summarized as follows. The protein in the urine and the number of the cellular and other formed elements did not decrease; in fact a transitory increase was observed after the treatment with cortisone was begun. Tests of renal function were interesting; the inulin clearance was low at the outset, but rose during the administration of the hormone, and tubular function, as estimated by secretion of para-aminohippurate, though normal or only slightly low before treatment, rose during the period, and then fell to the previous levels after the hormone was suspended. The clearance rate of para-aminohippurate and the renal blood flow were below normal at the beginning, but rose during the period. Shortly after treatment began there was a rise in temperature, and during the last few days of treatment puffiness of the face appeared. A significant retention of sodium was observed during the administration, and afterwards both sodium and water excretion increased considerably, and a rise of weight by two pounds which had occurred disappeared. The authors conclude that the improvement in renal function during the test appears to indicate a favourable effect on the pathological process, but any such effects seemed to be on the function of the kidneys only, and not on the inflammatory lesion or on the course of the disease. The functional *status quo* was resumed after the hormone therapy had been concluded, and subsequent observation showed that the boy made a good recovery. Protein had disappeared from the urine after less than three months, and in five months he was quite well, and there was no sign of residual damage to renal function.

The lack of beneficial effect on the course of the disease seems at first sight to be disappointing, but it cannot be said to be quite unexpected. In an editorial in the *Archives of Internal Medicine* it is pointed out that the increased feeling of well-being that is so striking a phenomenon in febrile patients treated with one of the active adrenal hormones tempts physicians to try these preparations in various infective diseases, but that the total course of such conditions is often unaffected, and complications are not prevented.[1] This has been observed in series of cases of pneumonia of various types in which a striking temporary remission was produced, but little else. In poliomyelitis, as the result of a pooled survey, it was found that the "alarm reaction" invariably occurred, but comparison with controls demonstrated no further benefits. Controlled experiments on animals have revealed much useful information concerning immunity reactions, but the early suppression of antibody formation suggests caution. Oswald Savage in an article traversing the present state of knowledge for the practising clinician points out that the now familiar side effects of these hormones need not *per se* cause alarm, though they are, as Hench has said, to be respected.[2] Still, the various psychic reactions, the retention of water and sodium, the loss of potassium from the blood, the hyperglycæmia and the production of the Cushing syndrome remind us of the potency of these remarkable substances. Moreover, they will not destroy infective agents or remove their toxic products. Savage aptly quotes Hench, whose aphorism is worth requoting: "They do not extinguish the fire or repair the damage, but provide an asbestos suit which protects the patient. As long as the protection is not discarded until the end of the natural duration of the disease, the patient remains well."

THE PREVENTION OF KERNICTERUS.

THE rapid growth of knowledge concerning *erythroblastosis fœtalis* and a certain degree of prophylaxis of this serious hazard of the newborn have not removed the anxiety that babies who recovered from the anæmia might succumb to damage to the brain. The possibility that even surviving infants might suffer from spastic paralysis and mental deficiency is also alarming. Prevention, of course, depends to a considerable extent upon knowledge of the pathology of the condition, though, as we have learnt from experience with other diseases, understanding of ætiology and pathology does not always give us the cure. Richard Day and Elise Perry have tried to produce evidence in favour or otherwise of the hypothesis of Wiener, who postulates an intravascular agglutination of red cells in the susceptible areas of the nervous system which impairs the circulation in the capillaries of the brain and produces anoxia.[3] The parallel with carbon monoxide poisoning is quoted in this connexion. It is significant that Wiener regards this suggested pathology as the basis of exchange transfusion in treatment. Day and Perry devised a set of experiments on rats complementary to some other observation which they had made. They found that intravascular agglutination could be demonstrated in a child of eleven months with hæmolytic anæmia who showed no sign of damage to the nervous system, and that hæmagglutination was not observed in a four-day-old baby dying from kernicterus. Experimentally they showed that intravascular agglutination in the jaundiced rat does not result in kernicterus, though it was admitted that no fall in the tissue oxygen tension could be observed. The rats were injected with anti-rat red cell serum, but rapid sedimentation of the red cells and intravascular agglutination were not necessarily associated with icterus. These experiments failed to shed light on the pathogenesis of kernicterus;

[1] *The New England Journal of Medicine*, December 28, 1950.

[1] *Archives of Internal Medicine*, January, 1951.
[2] *The Postgraduate Medical Journal*, February, 1951.
[3] *Blood*, December, 1950.

the authors remark that we still do not know what is the state of the supply of blood and oxygen to the cells of the basal ganglia in an infant the subject of kernicterus.

However, another team of workers has been examining the possibility of working out a programme of treatment for babies with erythroblastosis with a view to preventing the development of complications in the central nervous system. Fred H. Allen, Louis K. Diamond and Victor C. Vaughan have shown in previous reports based on a twelve-year study that kernicterus was the chief hazard to recovery in babies with the hæmolytic anæmia of the newborn.[1] They lay stress on the well-known fact that kernicterus is an acute affection occurring in early post-natal life, and does not occur in the stillborn. They further stress the importance of maturity of the infant as a safeguard against the occurrence of this dangerous condition. They have found that the adoption of exchange transfusions in the treatment of *erythrocytosis fœtalis* did not certainly affect the mortality rate or the complication of kernicterus. But it appeared that the avoidance of immaturity by not inducing labour before term in sensitized mothers was responsible for the lowering of mortality among the babies, and further that this improvement was due to the lessened number of cases in which nervous damage occurred after birth. Study of the relation of jaundice to kernicterus was informative. The degree of jaundice recorded in these observations was the maximum seen during the first five days of life. It being admitted that there are a number of variables present in those cases presenting signs of nervous involvement, the common denominator was found to be severe jaundice. As this in turn may be minimized by the giving of exchange transfusions, it seems that a rational prophylactic programme may be drawn up. This includes the avoidance of the induction of labour, the use of exchange transfusions for babies thought to be in risk, and the repetition of exchange transfusion when increasing jaundice appears following the first transfusion. The data on which the statistical deductions in this work have been based have been drawn from a study of 368 liveborn babies with blood of the Rh-positive type, whose mothers were sensitized Rh-negative. Although it seems difficult to produce convincing experimental evidence in support of a plan of treatment, the lines suggested here agree with the conclusions of Wiener, and are worthy of consideration.

RETINOPATHY IN MALIGNANT HYPERTENSION.

RETINAL CHANGES in hypertensive arterial disease have been recognized as important from the diagnostic and prognostic points of view, and, in the last quarter-century, as most significant in the syndrome known as malignant hypertension. It is twenty-six years since Norman M. Keith and Henry P. Wagener described a series of cases of severe hypertension, in which neuroretinitis was present, but in which the patients had adequate renal function. They noted that the disease ran a progressive course, and was often rapidly fatal. It is interesting now to read an article by the same authors, which describes a series of fifteen patients with malignant hypertension observed over a period of twenty years in whom recession of papillœdema and neuropathic changes has occurred.[2] They remark that during this period they have rarely seen cases of apparent spontaneous arrest of the condition, and that others have described similar events. One practical point about this experience is to determine whether this improvement in so serious a disease could be related to any specific form of treatment, for various surgical procedures have gained more vogue of recent years, and there are reports in the literature of lessening in the general and, in particular, the retinal signs following operations on the sympathetic nervous system and, in appropriate cases, unilateral nephrectomy. Simultaneously with the rising popularity of surgical measures great attention has been paid to special dietary methods. Of these the salt-low diet and the more publicized rice diet have received the most attention. Some writers have claimed success after the injection of tissue extracts or of bacterial pyrogens. Keith and Wagener's series, however, differed from others in that no such methods of treatment were employed. In three of their fifteen patients they thought that the use of thiocyanates might have played a part in the remission of symptoms, a claim which has been made by other workers in the field. With this exception no form of therapy was employed which could be given the credit of halting the pathological process.

Keith and Wagener point out that their series offers an unusual opportunity to review the course of malignant hypertension after the recession of a single objective finding of recognized importance. The ages of the patients varied from twenty-nine to sixty-two years at the time when papillœdema was first observed; the mean age was forty-six years. From the recognition of the retinal lesion until death a period elapsed ranging from two months to twelve years, and one patient was still actively working after nine years. Treatment consisted simply of the adoption of as calm a mode of life as possible, a moderate diet of the usual balanced type, without prohibitions, and the exhibition of some mild sedative. In other words the patients were carefully but not alarmingly doctored. Two patients were submitted to splanchnicectomy, but after the recession of the retinal signs. One patient was given some radiation of the hypophyseal area, but, although the ocular signs later became less, no causal connexion is claimed by the authors. Blood pressure readings were recorded in all cases. Though high systolic and diastolic pressures were observed, particularly the latter, consistently high blood pressures were not found in all, as is sometimes claimed. In fact, a labile blood pressure was recorded in half the patients.

One interesting feature of this series is that in some patients hypertension had been observed at the clinic for periods ranging from six weeks to eight years before the development of papillœdema. The importance of accurate and frequent retinal examination is stressed, and, although the ophthalmoscope is now an essential working tool of the physician, its value is in proportion to the assiduous care with which it is used. Five of the authors' patients out of eleven who complained of visual disturbances at the outset of clinical illness remarked improvement at a later date. Data are presented in this paper also about cerebral, cardiac and renal signs and symptoms. Attention is drawn also to the evidence provided by clinical and pathological surveys of the very widespread involvement of the arteriolar system. In six of the cases presented here this is strikingly demonstrated. Finally, the question of prognosis arises, for malignant hypertension carries an unusually bad outlook. Analysis of the whole clinical findings in this small but well-observed series showed that cardiac involvement occurred in nearly all, but that only one patient died from cardiac failure. Even mild cerebral episodes were significant, for they were observed in five of six patients who died of ingravescent lesions of the brain. Seven patients had considerable renal insufficiency, but only one died from uræmia.

The authors wonder if intensive functional studies of individual organs are advisable, in view of the variable distribution of lesions in the vast arteriolar system. They think it is logical to suppose that the retinal lesions are due to decompensation of the local circulation, but they do not think they are related to changes in the cerebrospinal fluid pressure, as seen in hypertensive encephalopathy. This concept brings us back to the hypothesis of ischæmia caused by spastic focal constrictions in arterioles which were not necessarily irreversible. There is at least reason to have more confidence in the adaptability of the vascular system, even under the strain of disease, and this series, which will fit into the experience of other physicians, shows that prognosis should not be subject to the prejudice of a name or label. Perhaps more interest might be taken by physicians in the clinical state and history of those patients who appear well, but who have patches of healed chorioiditis.

[1] *American Journal of Diseases of Children*, November, 1950.
[2] *Archives of Internal Medicine*, January, 1951.

Abstracts from Medical Literature.

OBSTETRICS AND GYNÆCOLOGY.

Double Uterus.

WILLIAM HUNTER (*The Journal of Obstetrics and Gynæcology of the British Empire*, October, 1950) discusses the causation, classification, incidence, diagnosis and treatment of double uterus and reports a series of 32 confirmed cases. A double uterus is defined as a uterus with two separate cavities in which neither horn is rudimentary. The author discusses various forms of developmental errors of the Müllerian ducts and the failure of fusion of these ducts. He classifies uterine deformities after the methods of Kaufmann and Way into four large groups: (i) those due to failure of approximation of the Müllerian ducts; (ii) those due to failure of fusion of the Müllerian ducts; (iii) those due to failure of both approximation and fusion of the Müllerian ducts; (iv) those due to complete or partial failure of development of the Müllerian ducts. In the series of 32 reported cases 13 were classified as *uterus bicornis bicorpus bicollis* and 13 were examples of *uterus bicornis bicorpus unicollis*. The author states that a double uterus usually lies in the anteverted position, muscular development of the uterus is normal, the capacity of each cavity approximates that of a normal uterus, and the blood supply has no special peculiarity. Cases of unilateral hæmatometra and pyometra have been described. The author assesses the incidence of double uterus at about 1 in 3000 cases, and considers that the deformity represents a reversion to a more primitive type of uterus or atavism. Many cases are symptomless and are unrecognized until discovered during pregnancy or labour or during investigation for dysmenorrhœa, dyspareunia, menorrhagia or abortion. There is frequently an associated sagittal vaginal septum, and the cervix may be single, septate or double. The author draws attention to the possibility of missing an incomplete abortion or carcinoma in an unexplored horn of an undiagnosed double uterus. The diagnosis of double uterus by vaginal examination may be difficult, and the use of a uterine sound or two uterine sounds is helpful. Hysterosalpingography is a valuable aid to diagnosis. Pregnancy in a double uterus is associated with an increased risk of abortion (40%), a high incidence of twin pregnancies, the premature onset of labour and more frequent complications of labour. Examples of superfœtation have been recorded, and there would appear to be an increased incidence of fœtal deformity.. Operative treatment is not justifiable simply for the correction of a uterine deformity, but metroplasty may be indicated in cases of repeated abortion.

Chorionepithelioma.

E. E. DILWORTH, C. R. MAYS AND L. A. HORNBUCKLE (*American Journal of Obstetrics and Gynecology*, October, 1950) report and discuss a study of 15 cases of chorionepithelioma. They consider the term chorionepithelioma misleading and have classified the cases into the following groups: syncytioma (one case), *chorioadenoma destruens* or invasive mole (three cases), choriocarcinoma (eleven cases). The mortality rate of the series was 73·3%, but all the patients with chorioadenoma and syncytioma survived and all with choriocarcinoma died. The authors state that clinical metastases are almost unknown in chorioadenoma, and the prognosis is good when the uterus is removed. The danger of death from this type of tumour is by perforation of the uterus with resulting hæmorrhage and infection. The authors consider removal of the ovaries unnecessary in this condition. In eleven cases of choriocarcinoma, all patients except one had metastatic lesions before operation. Autopsy studies in eight of these cases showed metastases in lungs, liver, vagina, brain, kidneys, bladder, urethra, ovary, skin, regional nodes, bowel, spleen and meninges. The authors found definite fallacies in curettage as a method of diagnosis. In one of four curettages performed, removed tissue did not afford the diagnosis because the tumour mass was placed deep in the wall of the uterus. From autopsy findings curettage would have been of no help in diagnosis in at least five of the eleven cases. In two of these the tumour was in the uterine tube and in three others it was intramural. Biological tests for pregnancy are not infallible in these cases, and the authors consider the spinal fluid Friedman test a poor substitute for the quantitative Friedman test. Abnormal and excessive uterine bleeding was the outstanding sign; it was present in nine of the eleven cases. Three cases of choriocarcinoma followed hydatidiform mole, three followed abortion, three followed full-term pregnancies and two followed tubal gestation. The authors state that the chief value of total hysterectomy in the choriocarcinoma group is that it prevents early death from uterine hæmorrhage and intercurrent infection. They consider that the presence of metastasis is no contra-indication to surgery and that the ovaries should not be removed in young patients with choriocarcinoma.

Time of Ovulation.

C. L. BUXTON AND E. T. ENGLE (*American Journal of Obstetrics and Gynecology*, September, 1950) discuss various indirect methods which have been used to determine the time of ovulation in women. These methods include the observation of changes in the epithelium of the genital tract, changes in urinary excretion of hormones and changes in the basal body temperature. All determinations of the ovulation time have disadvantages when required for clinical application. Urinary assays are difficult, and vaginal smear examinations require careful interpretation; endometrial biopsy and pregnandiol determinations can identify ovulation only when it has passed. The basal body temperature record affords the only practical means of fixing the time of ovulation at a clinically useful stage. The authors report observations on the ovary and the endometrium at the time of ovulation as indicated by the basal body temperature changes in 18 patients booked for elective operations. In this way they attempt to answer the question whether or not the temperature change is a sufficiently accurate index of the time of ovulation. All patients were submitted to operation (mostly for fibroid tumours) on the day on which their temperature charts showed the characteristic rise associated with ovulation. The endometrium was examined and the *corpus luteum* was excised and studied in the 18 cases. Analysis of these cases revealed the following findings: in six cases there was no definite evidence of ovulation, in two cases fresh *corpora lutea* were found, in four there were *corpora lutea* possibly twenty-four hours old, in two there were *corpora lutea* possibly thirty-six hours old, in two there were *corpora lutea* possibly forty-eight hours old, and in two there were *corpora lutea* possibly seventy-two hours old. The endometrium showed much less progressive change than the *corpora lutea*. The authors consider that there is a delay in the appearance of the secretory phase, and luteal activity on the endometrium did not appear in this series of cases until the *corpora lutea* were at least thirty-six hours old. They note a considerable difference in the histological patterns of both the endometrium and the excised *corpora lutea*, although all patients underwent operation on the morning of their basal temperature rise. They observe that the ovulatory temperature elevation is not entirely simultaneous with the time of ovulation, and that there is a variation of some three to four days in the age of the *corpus luteum* at this date. Even when the temperature rise is abrupt, the evidence presented indicates considerable inconsistencies in time relations (of up to four days) between temperature rise and luteal age. Patients who use temperature charts for determining the date of ovulation should, according to the authors, be told that this method affords only an approximate indication of the time of ovulation.

Spontaneous Intraperitoneal Hæmorrhage from the Superficial Veins of a Uterine Fibromyoma.

VYVYAN DAVIES (*The Journal of Obstetrics and Gynæcology of the British Empire*, April, 1950) reports two cases of severe intraperitoneal hæmorrhage following the spontaneous rupture of veins on the surface of uterine fibroid tumours. Although uterine fibroid tumours are so common and their ability to disturb the normal anatomy and vascular arrangements of the pelvis is well recognized, the author considers it surprising that less than 60 vascular catastrophes have been reported in the literature. The first case was that of a single woman, aged thirty-eight years, whose menstruation had been regular, who became suddenly faint and had generalized abdominal pain while sitting talking. Generalized tenderness of the abdomen was present, with a palpable tumour extending from the pelvis to midway between the *symphysis pubis* and the umbilicus. At operation the abdomen contained free fluid blood, and the uterus was found to be irregularly enlarged by multiple fibroid tumours. A large vein on the posterior surface of the largest fibroid tumour had ruptured and was still actively bleeding. On account of associated ovarian endometriosis bilateral salpingo-oophorectomy and supravaginal hysterectomy were performed and convalescence was uneventful. The second case was that of a biparous woman, aged fifty-one

years, who was menstruating regularly, and who had sudden acute abdominal pain while seated in a chair. The pain commenced in the lower part of the abdomen and spread to the epigastrium and left hypochondrium. Fainting and vomiting were associated features, and a diagnosis of ruptured peptic ulcer was made. The abdomen was opened through a right upper paramedian incision and the peritoneal cavity was found to be full of blood. No cause of the hæmorrhage was found in the upper part of the abdomen, but a uterine tumour was felt on exploration of the lower part of the abdomen. The incision was enlarged and a uterine fibroid tumour the size of an eighteen weeks' pregnancy was delivered. A ruptured vein was found on the posterior surface of this tumour. Supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed. The author observes that sudden increase in intraabdominal pressure is considered to be the usual precipitating cause of this complication, but was not a feature in the two cases described. Increased blood supply to the pelvic organs was the probable cause, since both patients were menstruating at the time of the hæmorrhage. The source of the hæmorrhage, usually a vein, is commonly situated on the posterior wall of the tumour and may not be quickly apparent on laparotomy. Supravaginal hysterectomy has been the commonest operative treatment in reported cases, but myomectomy has been performed on a few patients, and simple ligation of the bleeding vessel was the method of treatment of one patient.

Diabetes and Pregnancy.

R. A. REIS, E. J. DE COSTA AND M. D. ALLWESS (*American Journal of Obstetrics and Gynecology*, November, 1950) present a study of 163 pregnancies of 52 diabetic women delivered over a period of fifteen years at the Michael Reese Hospital, Chicago. Sixty-nine pregnancies occurred before the onset of diabetes and resulted in 13 abortions and 56 viable pregnancies with 52 living children, two stillbirths and two neo-natal deaths. The average birth weight was 3939 grammes. Thus there was an increased incidence of large babies, stillbirths and neonatal deaths in babies born during the pre-diabetic period. Twenty-two pregnancies occurred after the onset of diabetes in 14 patients who were not under the care of the authors. Fifty-two diabetic women had 70 pregnancies under supervision after the onset of diabetes; 11 pregnancies ended before the stage of viability of the child and 53 of the 59 viable babies were born alive. Two did not survive the neonatal period. The fœtal salvage of viable babies was 86·4%. The reported increased dangers to the fœtus of the diabetic woman from great increase in fœtal abnormalities, malposition, hydramnios and toxæmia were not found in this series. Fœtal abnormalities occurred in only one baby, malpresentation in seven cases, hydramnios in six. The method of delivery was determined as an obstetric problem: the *primigravida* with a long closed cervix was best delivered by Cæsarean section; the *multigravida* with a dilatable or dilated cervix was best delivered vaginally after induction of labour by simple rupture of the membranes. Excessive fœtal size, intact cervix or previous Cæsarean section were indications for section in the *multigravida*. Thirty-three were delivered by Cæsarean section and 26 vaginally. Decision as to time of delivery depends on the history and the determination of fœtal size. In general the fœtus of a diabetic woman will achieve a size of 3300 to 3700 grammes between the thirty-sixth and thirty-seventh weeks of pregnancy, and the danger of intrauterine death is ever present after the thirty-fifth week. The authors believe that three of their six stillbirths might have been averted if more attention had been paid to fœtal oversize and the pregnancy terminated. Histological examination of the placentæ showed no changes from those found in non-diabetic women. The incidence of toxæmia in the series was 10·2%. No toxæmias were severe, and no sex hormone therapy was used in any case. The authors regard such treatment as unnecessary. There was also no evidence of hypoovarianism in any patient. No patient complained of amenorrhœa or sterility. The authors state that premature vascular aging in the diabetic should be a contra-indication to pregnancy, and when pregnancy is allowed meticulous care is necessary. During pregnancy the insulin of choice is protamine-zinc because of its longer action. The amount used should be sufficient to prevent acetonuria, to maintain blood sugar at a lower level, to reduce the glycosuria, and to give the patient a sense of well-being. The maintenance of a slight amount of glycosuria, that is, up to 15 grammes per twenty-four hours, is generally permitted. Adequate dosage of insulin can be judged only by the results achieved. The insulin must be changed to regular insulin (*a*) whenever complications such as *hyperemesis gravidarum*, toxæmia or contraindications to regular food intake arise, (*b*) three to seven days before Cæsarean section or the induction of labour, (*c*) for the duration of delivery and (*d*) in the immediate puerperium. The regular insulin should be given in divided doses, and before each meal, the dose being regulated by glycosuria, blood sugar levels and ketosis. The authors found that the blood sugar level of the baby of a diabetic mother falls more rapidly (within one hour), falls lower and returns to normal more slowly than that of the baby of a normal mother. Successful management of the newborn baby demands that he be cared for as if he was a premature baby, regardless of age, size and weight. The three dangers are anoxia, lethargy and hypoglycæmia. The respiratory passages are cleared, oxygen is administered and 50% glucose solution is frequently administered by medicine dropper during the first hours of life. By these means the majority of babies can and should be saved.

Extraperitoneal Cæsarean Section.

F. R. STANSFIELD AND L. W. D. DRABBLE (*The Lancet*, January 13, 1951) review the alternative methods of management of the labour of women who are potentially or actually infected, and discuss the advantages and disadvantages of extraperitoneal Cæsarean section. They outline the operative technique. They consider that many of the failures to obtain satisfactory delivery can be eliminated by the use of extraperitoneal Cæsarean section. They state that the present trend towards a broadening of the range of indications for Cæsarean section has been justified by the results, and that the extraperitoneal approach to the uterus permits a further justifiable extension of the indications already accepted. At the same time it leads to a reduction in the total incidence of the operation, because the surgeon can safely allow a trial of labour to proceed far longer than is the present custom.

Cancer of the Cervix Uteri: Australian Results, 1930-1950.

H. H. SCHLINK (*The Journal of Obstetrics and Gynæcology of the British Empire*, October, 1950) records the five-year and ten-year results of treatment of cancer of the *cervix uteri* over the period 1930-1944 at the Royal Prince Alfred Hospital, Sydney. After reviewing results of treatment by adequate radiation therapy and treatment by radical Wertheim operation, the author considered that radiotherapy did not entirely eliminate all cancer cells from the cervix and had no effect on lymph nodes invaded by cancer cells. Accordingly, in 1930, he and his colleagues, C. L. Chapman and F. N. Chenhall, commenced a combined treatment of radium application to the cervix followed by Wertheim hysterectomy. A dose of 7000 milligramme hours of radium is given by intracavitary and vaginal application, and the uterus is extirpated some five weeks later. All cases have been proven by biopsy before treatment commenced, and the radium-treated uteri and lymph nodes have been submitted to pathological examination after operation. All patients in the series have been clinically grouped according to the League of Nations International Classification. The overall results with 532 patients examined and 511 patients treated are set out in tables. The five-year cure rate of all patients examined was 30·3% and the ten-year cure rate was 27·7%. The cure rate of treated patients was 31·5% (five-year cures) and 28·7% (ten-year cures). After exclusion of Group 4 cases the five-year survival rate after combined radium and surgical treatment was 54% and the five-year survival rate after treatment by radiotherapy alone was 18%. The operability rate was about 50% of all cases examined, and the operative mortality rate of the series was 4·3%. There was an immediate post-operative morbidity in 12 cases and a delayed morbidity in 16 cases. The nature of these post-operative complications is detailed in appendices. Microscopical examination of removed lymph nodes showed involvement in 15·8% of cases. The author observes that the hypogastric glands are most commonly the site of cancer spread and that the aortic and obturator glands are rarely involved. After a study of the published figures of reliable cancer clinics throughout the world, the author considers that there is a greater salvage of patients with cancer of the cervix by this method of combined radium and surgical treatment than in most other clinics. Improvement in results can be achieved by education of the profession in the early diagnosis of cervical cancer, education of women approaching the cancerous age, the establishment of preventive cancer clinics and the treatment of all doubtful and diagnosed cases in established cancer clinics.

British Medical Association News.

SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association, in association with the Pharmaceutical Society of Victoria and the Pharmaceutical Service Guild of Victoria, was held in the Medical Society Hall, 426 Albert Street, East Melbourne, on March 7, 1951. Papers were read by four pharmacists.

Pharmaceutical Benefits in Practice.

MR. F. N. LEE read a paper in which he discussed everyday problems met by prescribers and dispensers in the operation of the *Pharmaceutical Benefits Act*. He explained, by way of introduction, that the discussion would deal only with practical problems that arose from day today; political aspects of the subject were outside the scope of the evening's discussion. The present Page plan for pharmaceutical benefits had been operating for six months. Some might have different views about the scheme according to their political views, but both professions had accepted the scheme, and the purpose of the discussion was to see if they could make it work just a little more smoothly for the medical profession, the pharmaceutical profession and the Health Department. One could not play a game of cricket or golf without rules. The scheme or plan for pharmaceutical benefits had some rules—some of them appeared to be irksome, some might appear unnecessary, but from the point of view of the department trying to run the scheme, observance of all the rules was vitally necessary to make the machine turn over smoothly.

Referring first of all to the prescription form, Mr. Lee pointed out that two types of form were being used—the official government form and the private form of the prescriber. With the government form there was a margin on the left-hand side which the chemist used to insert the serial number of the prescription, the code number of the item dispensed, and the price. The forms were in duplicate, and to the dispenser each was clearly marked so that the original and duplicate were not easily mixed. That was important to the chemist because the Health Department would pay only on originals; duplicates were for the chemists' own records. Government forms did not have to be specially endorsed by the prescriber "Pharmaceutical Benefits", but when prescribers used their own private forms, it was necessary to see that all the details were inserted on each form similarly to what was done on government forms: the name and address of the patient, the name and address of the prescriber, the endorsement "Pharmaceutical Benefits", the date, the doctor's signature, and finally, not more than two benefits on one form. It would help the chemist if the doctor left him about one inch of margin on the left-hand side of the form for the details of the prescription as set out previously.

Mr. Lee pointed out the following pitfalls that might occur in connexion with the prescription forms when prescribers used their own private forms. The first was forgetting to endorse the form "Pharmaceutical Benefits". The second was omitting to sign in full; initials, so often used on lodge book prescriptions, were not enough for a pharmaceutical benefits prescription. The third pitfall was omitting to mark the carbon copy "duplicate". The last occurred with forms printed with "duplicate" on each alternate sheet, when the doctor used an "original" to write a private prescription, then proceeded to write a pharmaceutical benefits item without tearing out the unused "duplicate". The result was an "original" written on a form marked "duplicate" and a carbon copy on an "original" form. The only trouble was that the chemist did not get paid. To safeguard the Treasury, the regulations stated that payment would be made only on "originals" and that carbon copies would not be accepted as "originals". In such cases the chemist must return the prescription to be rewritten. The remedy seemed to be to have prescription pads made up with coloured sheets for duplicates interleaved with the white forms. That plan was in operation in a number of surgeries and was helpful to both doctor and chemist.

Mr. Lee next considered branded drugs and explained that when the prescriber wished to specifiy a special brand (which, of course, must be one of those which were already included in the official list of brands issued by the Health Department) he might do so. When new brands were included, they all heard rumours from trade representatives before the official lists were circulated, but such rumours should be ignored until official advice was received. Trade representatives could not beat the pistol like that, because the chemist could not dispense the item at government expense until the advice was in their possession. When a person presented a prescription for a branded drug, supplies of which were not available through the usual channels, the chemist had two alternatives: to get in touch with the doctor and seek permission to cancel the brand shown in the prescription (in which case, the price of the cheapest listed product available would be paid), or when the doctor required another brand, to return the prescription to the prescriber for his endorsement. When a doctor did not indicate on the prescription any particular brand to be supplied, the rules provided that the price of the cheapest listed drug (basic price) as shown in "The Table" would be paid. A recent amendment to the regulations provided that where the cheapest branded drug was not available through the usual wholesale channels, the basic price might be raised to the price of the next higher brand available. That instruction, however, would not apply in cases of a temporary local shortage. The purpose of the amendment was to provide for cases in which, firstly, certain brands were not available through the usual source of supply (wholesale) or, secondly, there was a general shortage brought about by an inability of the manufacturers to obtain stock of the drug or raw materials. Any claim for the payment of a higher rate in the first cases must be supported by evidence of the inability of the wholesaler to supply. In respect of the second cases, when the absence of stock was known to the department, no further evidence would be required.

Speaking on the subject of dangerous drugs, Mr. Lee pointed out that when a dangerous drug was ordered it must not be ordered on a form with any other benefit. If some other item was ordered on the same form as a dangerous drug, the patient must either pay the chemist for it, or return to the doctor to have the prescription rewritten.

Mr. Lee commented on the regulation requiring the prescription of only two benefits per form, and referred to several popular traps that might occur. Item 108, "Myocrisin", prescribed in four separate doses, one ampoule of each dose, was four benefits and the prescription should be written on two separate forms, two per form. Item 89, Pertussis Vaccine Phase 1, prescribed as one ampoule of each of "A", "B" and "C" strength, was three benefits, but prescribed as "A" one ampoule and "B" two ampoules, it was only two benefits. The Health Department paid for only two benefits on any prescription, so the third must be paid for by the patient or else he had to return to the prescriber to have a new prescription for the extra benefit.

Multiple carbon copies were next mentioned. Mr. Lee said that in cases in which repeats were not allowed and a new prescription was required for each fresh supply, the practice of inserting the requisite number of carbon sheets to produce the extra prescriptions was useless because only the number 1 sheet was a true original; number 3 and number 5 *et cetera*, being carbon copies, even if signed separately and dated correctly, would not be paid.

Mr. Lee said that a new issue of the booklet was due in March with all amendments and new drugs to date. In addition, a loose leaf book of convenient size with a leatherette cover was in course of preparation and would be distributed as soon as ready. That would make it possible for alterations and additions to be inserted as a new sheet, and the obsolete sheets could be discarded.

Mr. Lee then referred to a new problem that had arisen. He said that in all its dealings with the Government, the pharmaceutical profession had refused to give any free service to the Government. They had argued and won their case that all services must be paid for at recognized rates. Under the *Pharmaceutical Benefits Act* many cases had occurred in which a prescriber ordered for a patient ingredients for a prescription which were provided free under the Act, and then ordered them to be dispensed to make, say, eye drops, or a mixture, or perhaps an ointment. The Guild had directed members that they should charge the appropriate dispensing fee and container charge to the patient in all such cases. A number of cases had been reported to the Guild in which patients had clearly indicated that the prescriber had told them that the prescription would be free. For instance, penicillin 15,000 units with normal saline two millilitres was ordered on a pharmaceutical benefits prescription; then either on the same form or on another form, directions were given for preparing eye drops, to be used every three hours. An argument ensued with the patient because a charge was made for dispensing the eye drops. Pharmacists were concerned, and they asked for the sympathetic understanding of the medical profession in such cases. The Government provided only the

ingredients of the prescription free, but in all cases appropriate charges according to the Guild scale of fees would be made for the actual dispensing involved. Mr. Lee asked doctors who did write such prescriptions to be sure not to give the patient the impression that the eye drops *et cetera* would be without charge. Another development of the same problem had cropped up, only this time the prescriber told the patients to mix their own drops. Penicillin and saline or distilled water were ordered on a pharmaceutical benefits form and were free. The patient was then told to break the ampoule and mix the contents with the penicillin in the bottle and use the mixture for drops *et cetera*. It appeared that this practice had grown up in a particular district, because the chemists were carrying out Guild instructions to charge Guild fees for dispensing the drops. It did appear a very debatable ethical point. Could an untrained person without any skill at all prepare a sterile preparation for administration? In the event of any trouble occurring, the chemist who supplied the products on the pharmaceutical benefits prescription could not be held responsible. It would be a matter between prescriber and patient.

On the subject of late fees, Mr. Lee pointed out that chemists were permitted to charge an after-hour fee for service outside regular business hours.

Finally, Mr. Lee referred to the prescription of non-benefits on government forms. He said that a number of complaints had appeared in letters to the newspapers to the effect that chemists had been charging for "free" medicine prescriptions. In his brief outline he had shown how some of those complaints could arise. Yet another trap of that kind was the writing of non-benefits on official government forms. Recently Mr. Lee had been handed three official forms by a patient—one for senega and ammonia, the second for sulphur ointment, and the third for "Trisulpha" tablets. The first two were useless as government prescriptions and should have been written on a private form. The patient was very hostile; he knew that they were pharmaceutical benefit forms and challenged the right to charge.

Mr. Lee appealed to both chemists and doctors to work more closely together to endeavour to by-pass the pitfalls that had been mentioned, and even if they did object to the red tape and restrictions, to try to look at it like a game of cricket or golf. If they tried to learn the rules and play according to the rules, the whole scheme would work a great deal more smoothly.

Emulsion Cream Bases.

MR. A. W. CALLISTER read a paper on emulsion cream bases. He pointed out that the development of emulsified bases for external application was of mutual interest to prescriber and dispenser. Prepared from "surface active" materials, they were usually almost neutral, non-irritant preparations with many advantages over the old ointment bases. Products made with such agents were easy to spread, easily removed, odourless and non-sticky; they did not restrict evaporation and perspiration, gave improved contact with skin and transferred medicaments more rapidly to the tissues. Of the properties mentioned, the delivery of medicaments was most important. Improved skin contact and absorption were due to the surface action of the emulsifier, the reduction of surface tension of the liquids in the emulsion. Because an oil-in-water emulsion base was more readily miscible with body fluids, that type of vehicle would transfer medicaments more rapidly than the water-in-oil emulsion base.

Classification of emulsifying agents might be based on their dissociation in aqueous solution. Thus there would be anionic emulsifiers, in which the surface activity was due to the negative "ion", for example, soaps and emulsifying wax; cationic emulsifiers, in which the positive "ion" was surface active, for example, C.T.A.B. ("Cetavlon") and "Zephiran"; and non-ionic emulsifiers, which did not ionize, for example, sorbitol derivatives ("Spans" or "Tweens"), cellulose derivatives and polyethylene glycols. The classification excluded the following widely used emulsifiers: emulsifiers from vegetable sources; emulsifiers from animal sources, such as wool alcohols and beeswax; finely dispersed solids, such as bentonite.

Anionic emulsifiers, such as emulsifying wax (British Pharmacopœia), were widely used. Probably the best example was the base used for *Cremor Penicillini* B.P., containing emulsifying wax 9%, paraffins 21% and water 70%. By varying the oily ingredients, for example, replacing the paraffins with a fixed oil, or by adding a little *Adeps Lanæ*, a variety of absorptive bases of different texture might be obtained.

Cationic emulsifiers were not as generally used in Australia, though "Cetavlon" as a primary emulsifier combined with various stabilizers such as cetyl alcohol was often referred to in overseas publications. This type of emulsifier was incompatible with the anionic agents, and the two should not be prescribed in the same formula.

The non-ionic emulsifiers had fewer incompatibles than the preceding types and were likely to have a wide use. They were usually available in a series showing a progressive rise in molecular weight, and giving a corresponding increase in density of the product formed.

Oil-in-water emulsion bases were frequently prescribed as "barrier creams". There might be many different types of barrier cream, for example, a cream to repel oil or grease, or one to repel acid, or a certain metallic irritant; all of these were barrier creams. It was preferable to specify a typical formula, such as hydrous emulsifying ointment (British Pharmacopœia) or one of the cream bases of the Australian Pharmaceutical Formulary.

For the protective type of base the British Pharmacopœia included hydrous ointment, prepared from wool alcohols. That ointment was a mixture of paraffins with wool alcohols and contained 50% of water. Wool alcohols freed from the fatty portions of *Adeps Lanæ* gave a product which was not sticky and had no objectionable odour, and in it the water was emulsified in the oily base. There also the use of fixed oil in place of some or all of the paraffin gave a variation of texture to suit an individual case.

Mr. Callister said that the emulsion cream bases were suitable vehicles for a wide range of medicaments. The antibiotics and the sulphanilamide derivatives were best presented in an oil-in-water base such as hydrous emulsifying ointment (British Pharmacopœia) or *Cremor Cereæ Sulphonatæ* (Australian Pharmaceutical Formulary). Those bases were suitable also for hydroxyquinoline derivatives, such as "Vioform", and for many organic materials both solid and liquid. Because of more rapid absorption of medicament, skin irritants should be used in lower percentages than when combined with fatty non-absorbent bases.

Incompatibility and Dosage.

MR. N. C. MANNING read a paper on incompatibility and dosage. He said that the problem of incompatibility was the same basically as it had been fifty years before, except that materials and dosage forms of medicines had altered tremendously. Previously pharmaceutical science had been concerned with the reaction between alkaloids and tannins, between spirits of nitrous ether and potassium iodide, between aromatic spirit of ammonia and mercuric chloride. Today mercuric chloride was not used for systemic infections, but the sulphonamide drugs had to a large degree superseded it. With the sulphonamides and other newer drugs had also come the associated problems of incompatibility in their everyday medical use. Sulphonamides were incompatible with the hypochlorite solutions when used topically. Vitamin *B* was incompatible with some iron compounds. Phenobarbitone combined with theophylline with ethylenediamine. Penicillin was inactivated by many substances and conditions. The germicides used in sterilization operations had brought the problem of incompatibility to a popular dose form, the injectable. But in the limits of a short talk, Mr. Manning suggested they should take one specific example to illustrate the point that incompatibility was far from a "dead" topic, even in a world of stock tablets and ampoules.

Substances related to 7-hydroxyquinoline had come into wide use in medical practice and in pharmaceutical manufacturing. Because of their great reactivity with even small quantities of metallic cation, their incorporation with ointment and emulsion bases reenacted the four difficulties in dispensing salicylic acid and iodine. Even calcium hydroxide, a constituent of zinc cream, would react with and to some degree inactivate that type of compound. The pharmacist, per medium of formularies and by direct contact with the prescriber, could contribute to the overcoming of those difficulties.

Turning to the subject of dosage, Mr. Manning said that in its various aspects, dosage was more complicated today than ever before. There were four aspects of the topic which seemed to be of mutual interest to the practitioners of the two professions.

The first was that more factors were recognized as affecting dosage. In addition to the usually recognized factors of age, sex, disposition, tolerance, susceptibility *et cetera*, they were today very much concerned with duration of treatment, size of initial dose, size of maintenance dose, time of administration and, most important, weight with regard to infant dosage. The body weight of a child was

a useful guide to the pharmacist, particularly when there was a big disparity between body weight and age. Especially was that so in the case of strong doses of hypnotic drugs. Cumulative drugs of the arsenic, colchicine type were sometimes a worry to the pharmacist lest the treatment be continued without the knowledge of the prescriber.

The second aspect was that methods of administering drugs had become more complicated. Dosage forms were today very various. Apart from all the customary forms there were many methods of introducing drugs parenterally—intravenous, subcutaneous, intramuscular, intrathecal, and many others. It was helpful in pharmaceutical practice if the dosage form was indicated by the prescriber; for example, the route of administration and the final volume to be injected often determined the amount of chlorocresol or other bactericide which might be used by the pharmacist in the sterilization process.

The third aspect brought forward by Mr. Manning was that drugs were more potent than they had been. There was often a smaller gap between the therapeutic dose and the toxic dose, for example, in the sulphonamide drugs. In that regard the prescriber assisted the dispenser by giving specific directions. Mr. Manning commented that in examining the drugs in use today one was impressed with their potent character. They had graduated, as it were, from calvesfoot jelly to "Carbachol", from sulphur and molasses to sulphamerazine, from cubebs to curare. The fourth aspect was that multiple drugs were being ordered again. Development had been away from the prescription containing about a dozen ingredients to one containing a single active drug; but in modern times a slight trend back to the use of multiple drugs was noticeable. The ordering of a short-acting and a long-acting barbiturate together was often sound prescribing. A drug which would synergize and perhaps give a summated effect might be desired. The use of physiological saline solutions, the use of preserving agents in eye preparations, creams and injections were again widening the field of complex dosage systems and incompatibilities. Mr. Manning said that pharmacists still took pride in dispensing that most personal and legendary order of the physician, the prescription. The prescription had been described as the very cornerstone of the entire arch of therapeutic endeavour, resting upon the diagnosis and prognosis of the case on the one hand and upon the physician's knowledge of pharmacology and therapeutics on the other. If that was a true picture of the prescription, then perhaps the pharmacist's role was to erect the scaffolding that enabled the two sides of the arch to be firmly met.

Mr. Manning showed a series of specimen prescriptions to illustrate the various points of his address.

Dangerous Drugs and Poisons Regulations.

MR. H. A. BRAITHWAITE said that he had been asked to discuss the errors of commission and omission in interpretation of dangerous drug and poison regulations. However, rather than talk of sins and errors, he proposed to sketch out the main prescription controls on drugs and expected the problems and queries raised in discussion to fill out the subject of his talk. He said that the schedule to the *Poisons Act* that had most effect on the prescriptions of medical practitioners and on the dispensing records of pharmacists was the sixth schedule. That schedule was divided into two parts. The items in the first part were classified as dangerous drugs. That classification had come into being in the early 1920's at the request of the League of Nations, and with the dangerous drug regulations was intended to help stop addiction to those drugs. The second part of the schedule listed sedatives such as the barbiturates, the ergot preparations, the sulphonamides *et cetera*, and those items were known as specified drugs. All items in both parts of the schedule could be legally supplied for actual patients only through a pharmacist and on a medical practitioner's prescription.

Mr. Braithwaite went on to say that the various poisons schedules had, in recent years, been amended and added to by the Pharmacy Board only after consideration and recommendation by a Poisons Advisory Panel that included Dr. B. L. Stanton (nominated by the British Medical Association), Professor Frank Shaw (nominated by the university), Dr. Shiels (nominated by the Health Department), the Chief Officer of the Chemistry Information Section of the Commonwealth Scientific and Industrial Research Organization, Mr. Jewel, of the Department of Agriculture, Mr. Sissons, Dean of the Pharmacy College, Mr. A. W. Callister, Lecturer in Pharmaceutics at the Pharmacy College, the Chief Inspector of the Pharmacy Board, and two members of the Board itself. As the Pharmacy Board was an autonomous body it acted in all those matters without being subjected to political pressure.

The items called dangerous drugs that were listed in the first part of the sixth schedule were opium and its preparations, morphine and its salts and preparations, heroin and its salts and preparations, cocaine and its salts and preparations, extract and tincture of Indian hemp and the newer drugs amidone and pethidine. Amidone had some proprietary names; "Physeptone" was one. Pethidine was marketed under the names of "Doltantin", "Dolantol" and "Demerol". "Heptalgin" was similar to those drugs. All the dangerous drugs should reach a patient only after being supplied by a pharmacist on the prescription of a medical practitioner. That prescription must be cancelled and retained by the pharmacist, but if the medical practitioner wanted his patient to have any repetition of the prescription he might provide for up to three repeats; while in a chronic case an order to a chemist in the form of a certificate would be valid for a maximum period of six months. If a liquid preparation of morphine or heroin was wanted for a patient it was simple for the medical practitioner to write his prescription in a concentration outside the schedule. As an example, a linctus containing not more than a sixteenth of a grain of diamorphine hydrochloride in each 60 minims need not be cancelled. Similarly liquid preparations could contain a little more than 120 minims of *Liquor Morphinæ Hydrochloridi* in a fluid ounce before their prescriptions were cancelled.

The second part of the sixth schedule, that relating to the specified drugs, included all the barbiturates, chloral hydrate, amphetamine, the ergots, paraldehyde, and the sulphonamides. Prescriptions for those drugs might be dispensed only once unless the prescriber indicated otherwise. If the prescriber did order repetitions, the prescription had a total life of six months before cancellation. That was considered by the Poisons Advisory Panel as a long enough period for patients requiring sedation to go between visits to their medical adviser. Recently the antiepileptics, phenytoin ("Dilantin") and similar drugs, had been added to the schedule. Some other drugs included in the schedule to put them on a prescription basis, though the prescriptions were not subject to cancellation, were the antibiotics, the antihistaminic drugs and the thiouracils. Also covered by the specified drug schedule were some combinations of barbiturates with an approved therapeutic denaturant. In that group came such things as compound theobromine, tablets, ephedrine and phenobarbital combinations *et cetera*. The basis for that relaxation was provision of those items for certain chronic conditions that were not likely to change for many months; thus they could be treated without repeated calls on a medical practitioner.

Mr. Braithwaite said that at the present moment the members of the Poisons Advisory Panel were considering ways and means of providing a blanket control on all new drugs until they were proved safe and also free from unwanted side reactions, but that was not easy to provide for in law, as a substance must be known to be a poison before it could be controlled under the present legislation. He had mentioned that to show that they were trying to maintain safe handling of all drugs as they became available.

In conclusion, Mr. Braithwaite suggested that if a busy medical practitioner wished to provide for any prolonged treatment for a patient, so as to save himself time and the patient expense, the matter should be talked over with the local pharmacist. He should be able to show how six-month certificates and repeat prescriptions could be written.

Post-Graduate Work.

THE MELBOURNE PERMANENT POST-GRADUATE COMMITTEE.

PROGRAMME FOR JUNE.

Courses for Higher Degrees and Diplomas Part II.

A COURSE in cardiology, under the direction of Dr. Frank J. Niall, will be held at 2 p.m. on the following dates: June 5—Dr. M. V. Clarke, "Diseases of the Auriculo-Ventricular Valves", at Saint Vincent's Hospital; June 7—Dr. J. T. Cahill, "Prognosis in Congestive Cardiac Failure", at Saint Vincent's Hospital; June 12—Dr. K. Grice, "Diseases of the Aortic Valve", at the Royal Melbourne Hospital; June 14—Dr. L. Rothstadt, "Some Aspects of Coronary Disease", at the Royal Melbourne Hospital; June 19—Dr. M. Davis, "Total Therapy in Heart Disease", at the Alfred Hospital; June 21—Dr. H. B. Kay, "The Assessment of Systolic Bruits

with Special Reference to Congenital Defects", at the Alfred Hospital. The fee for this course is £3 3s., or 10s. 6d. per demonstration.

A course in gastro-intestinal disorders, under the direction of Dr. Roderick Andrew, will be held at 2 p.m. on the following dates: June 26—Dr. R. Andrew, "Chronic Diarrhœa", at the Alfred Hospital; June 28—Dr. P. J. Parsons, "Peptic Ulcer", at the Alfred Hospital; July 3—Dr. R. Doig, "Gastritis", at the Royal Melbourne Hospital; July 5—Dr. Howard Williams, "Diseases of the Pancreas", at the Children's Hospital; July 10—Dr. W. E. King, "Hepatitis", at the Royal Melbourne Hospital. The fee for this course is £2 16s. 2d., or 10s. 6d. per demonstration.

Courses for Higher Degrees and Diplomas Part I.

Courses suitable for candidates for Part I of higher degrees and diplomas will be continued at university departments.

Country Courses.

Mooroopna.

A course will be held on June 16-17 at the Mooroopna Hospital. The programme is as follows: Saturday, June 16—2.30 p.m., Dr. R. Orton, "Anæsthetics in General Practice"; 4 p.m., Dr. C. H. Fitts, "Disability of Chronic Cough". Sunday, June 17—10.15 a.m., Dr. A. R. Wakefield, "Skin Replacement in Relation to Injury"; 11.30 a.m., Dr. E. B. Drevermann, "The Use and Abuse of Intravenous Infusions". The fee for this course is £2 2s., or 10s. 6d. per lecture, and enrolments should be made with Dr. B. R. Schloeffel, honorary secretary of the Goulburn Valley Subdivision of the British Medical Association, Maud Street, Shepparton. Telephone 67.

Demonstration at Flinders Naval Depot.

A demonstration will be given by Mr. Douglas Duffy on Wednesday, June 13, at 2.30 p.m., on "Investigations in the Treatment of Common Urological Conditions". This will be given at the Flinders Naval Depot by arrangement with the Royal Australian Navy.

Enrolments.

Enrolments for metropolitan courses should be made with the Secretary of the Post-Graduate Committee, 394 Albert Street, East Melbourne. Telephone JM 1547-8.

Overseas Lecturers.

Attention is drawn to lectures by Professor B. W. Windeyer and Dr. M. H. Jupe, which the College of Radiologists (Aust. and N.Z.) is conducting at the Royal Melbourne Hospital main lecture theatre at 8.15 p.m. on Thursday, June 7, 1951. Professor Windeyer will speak on "The Place of Radiotherapy in the Treatment of Malignant Disease", and Dr. Jupe on "The Influence of Diagnostic Radiology in Medicine". All interested are invited to attend. The lectures are free of charge.

Naval, Military and Air Force.

APPOINTMENTS.

THE following appointments, promotions *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 22, of April 2, 1951.

NAVAL FORCES OF THE COMMONWEALTH.

Citizen Naval Forces of the Commonwealth.

Royal Australian Naval Volunteer Reserve.

Promotions.—Surgeon Lieutenants Peter Eric Blaubaum and Russell Geoffrey Cole are promoted to the rank of Surgeon Lieutenant-Commander, dated 20th November, 1950. Surgeon Lieutenant Ronald Mackenzie Macintosh, M.B.E., is promoted to the rank of Surgeon Lieutenant-Commander, dated 26th November, 1950.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED APRIL 7, 1951.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.[2]	Australian Capital Territory.	Australia.[3]
Ankylostomiasis	*	..	1	..	..	..	..	..	1
Anthrax	*	..	..	..	..	..	..	..	..
Beriberi	*	*	*	*	*	*	..	*	..
Bilharziasis	*	..	..	..	..	..	..	..	..
Cerebro-spinal Meningitis	..	..	1	..	..	1(1)	..	..	2
Cholera	..	..	..	..	..	..	..	..	..
Coastal Fever(*a*)	*	*	..	*	*	*	*	*	..
Dengue	*	*	*	*	*	*	..	*	..
Diarrhœa (Infantile)	..	..	5(5)	..	3(2)	..	..	..	8
Diphtheria	11(2)	5(2)	4(3)	..	3	..	..	..	23
Dysentery (Amœbic)	*	..	..	..	..	..	..	..	..
Dysentery (Bacillary)	*	2(2)	1	..	1	..	..	2	6
Encephalitis Lethargica	..	3	1(1)	..	..	..	..	..	4
Erysipelas	*	*	*	..	*	*	..	..	..
Filariasis	*	..	..	..	..	..	..	..	..
Helminthiasis	*	..	*	*	*	*	*	*	..
Hydatid	*	..	*	*	..	1	*	..	1
Influenza	*	*	*	1(1)	*	*	..	*	1
Lead Poisoning	*	*	..	*	*	*	*	*	..
Leprosy	..	..	..	..	..	..	..	..	..
Malaria(*b*)	*	..	1(1)	..	..	..	..	..	1
Measles	*	*	*	26(7)	*	*	..	..	26
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	65(34)	21(7)	57(12)	28(23)	1(1)	..	..	..	172
Psittacosis	*	..	*	..	*	*	*	*	..
Puerperal Fever	1	..	..	1(1)	..	..	..	..	2
Rubella(*c*)	*	*	..	*	1(1)	*	..	..	1
Scarlet Fever	15(3)	34(14)	5(3)	6	1(1)	4(4)	..	..	65
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	*	2	1(1)	*	*	*	*	*	3
Trachoma	*	..	*	*	*	*	*	*	..
Tuberculosis(*d*)	31(23)	24(20)	8(7)	2(2)	7(7)	8(3)	..	..	80
Typhoid Fever(*e*)	..	..	..	..	1	..	..	..	1
Typhus (Endemic)(*f*)	..	..	..	..	1(1)	..	..	..	1
Undulant Fever	..	..	..	..	..	..	..	..	..
Weil's Disease(*g*)	*	*	*	*	*	*	*	*	..
Whooping Cough	*	*	*	4(4)	*	*	..	..	4
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] The form of this table is taken from the *Official Year Book of the Commonwealth of Australia*, Number 37, 1946–1947. Figures in parentheses are those for the metropolitan area.
[2] Figures not available.
[3] Figures incomplete owing to absence of returns from the Northern Territory.
* Not notifiable.
(*a*) Includes Mossman and Sarina fevers. (*b*) Mainly relapses among servicemen infected overseas. (*c*) Notifiable disease in Queensland in females aged over fourteen years. (*d*) Includes all forms. (*e*) Includes enteric fever, paratyphoid fevers and other Salmonella infections. (*f*) Includes scrub, murine and tick typhus. (*g*) Includes leptospiroses, Weil's and para-Weil's disease.

AUSTRALIAN MILITARY FORCES.

Permanent Military Forces.

Royal Australian Army Medical Corps.

The age of retirement of 2/66 Major J. R. Nimmo has been extended to December 30, 1951.

Citizen Military Forces.

Eastern Command: Second Military District.

Royal Australian Army Medical Corps (Medical).—2/146528 Lieutenant-Colonel E. J. C. Molesworth, M.C., is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (2nd Military District), 21st November, 1950. 2/126997 Major G. V. Mutton is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (2nd Military District), 24th November, 1950. To be Captain (provisionally), 31st January, 1951: 2/70937 Alan Lacey Hellestrand.

Southern Command: Third Military District.

Royal Australian Army Medical Corps (Medical).—3/101802 Major R. A. Douglas is seconded for post-graduate studies in the United Kingdom, 15th January, 1951.

Reserve Citizen Military Forces.

Royal Australian Army Medical Corps (Medical).

2nd Military District: To be Honorary Captains.—Richard John Saunders, David Clarkson Maddison and Bruce Samuel Pearson, 23rd January, 1951, and John George Markus, 31st January, 1951.

4th Military District: To be Honorary Captain, 21st January, 1951.—Lehonde Lucas Hoare.

6th Military District: To be Lieutenant-Colonel, 21st January, 1951.—John Edis Edis.

ROYAL AUSTRALIAN AIR FORCE.

Permanent Air Forces.

Medical Branch.

Ronald Edward Robins (012652) is appointed to a short-service commission, on probation for a period of twelve months, 12th February, 1951, with the rank of Flying Officer.

The probationary appointment of Flight-Lieutenant L. A. Watson (034058) is confirmed.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Gunton, Peter Elliot, M.B., B.S., 1951 (Univ. Sydney), Ryde District Soldiers' Memorial Hospital, Eastwood.

Rogers, James Stewart, M.B., B.S., 1951 (Univ. Sydney), Mater Misericordiæ Hospital, Crow's Nest.

Pullen, Peter David, M.B., B.S., 1951 (Univ. Sydney), Ryde District Soldiers' Memorial Hospital, Eastwood.

Anderson, Hugh Cairns, M.B., B.S., 1951 (Univ. Sydney), Wellington District Hospital, Wellington.

Cooke, Kenneth Henry Stephen, M.B., B.S., 1951 (Univ. Sydney), 26 Dunmore Street, Bexley.

Leckie, Bruce Douglas, M.B., B.S., 1950 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.

Obituary.

JOHN LEO KING.

WE regret to announce the death of Dr. John Leo King, which occurred on April 15, 1951, at Melbourne.

ANDREW PINKERTON CRAWFORD.

WE regret to announce the death of Dr. Andrew Pinkerton Crawford, which occurred on April 21, 1951, at Brisbane.

GODFREY UNWIN TAYLOR.

WE regret to announce the death of Dr. Godfrey Unwin Taylor, which occurred on April 9, 1951, at Port Arlington, Victoria.

ALEXANDER JOSEPH MacDONALD.

WE regret to announce the death of Dr. Alexander Joseph MacDonald, which occurred on March 30, 1951, at Brisbane.

Diary for the Month.

MAY 8.—New South Wales Branch, B.M.A.: Organization and Science Committee.
MAY 11.—Queensland Branch, B.M.A.: Council Meeting.
MAY 15.—New South Wales Branch, B.M.A.: Medical Politics Committee.
MAY 16.—Western Australian Branch, B.M.A.: General Meeting.
MAY 17.—Victorian Branch, B.M.A.: Executive Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney)—All contract practice appointments in New South Wales.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in the Commonwealth can become subscribers to the journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £4 *per annum* within Australia and the British Commonwealth of Nations, and £5 *per annum* within America and foreign countries, payable in advance.

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Table of Contents.

[The Whole of the Literary Matter in THE MEDICAL JOURNAL OF AUSTRALIA is Copyright.]

REPORT OF A MANTOUX SURVEY OF "DISPLACED PERSONS" MIGRANT CHILDREN.

By J. P. VAN LEENT and P. F. HOPKINS,
Commonwealth Department of Health, Sydney.

DURING the year 1949 the flow of migrants from the displaced persons camps of Europe to Australia became well established, and in that year 20,970 adults and 5844 children arrived in the Reception Centre at Bathurst, New South Wales. They had previously spent many months in the displaced persons camps of Italy and Germany and then had followed a six-weeks journey to Australia under the crowded conditions which sea travel makes inevitable.

From the work of McDougall (1949) it was known that tuberculosis was common in the displaced persons camps from which our migrants were drawn; three separate X-ray surveys of the adults in these camps revealed a morbidity of 24 per 1000, 18 per 1000, and 19 per 1000 respectively. With this in mind it became health department policy to examine radiologically each migrant above the age of sixteen years immediately upon arrival at the Reception Centre. This was done by means of the 35-millimetre film technique, and in all doubtful cases further investigation with full-sized films was undertaken.

As a result it was discovered that among migrants entering the Bathurst centre in 1949, 357 "New Australians", representing 17 per 1000, were suffering from some form of pulmonary tuberculosis. Of these, 88 were admitted to full sanatorium treatment as "moderately or far advanced cases".

We became interested in the children of this group, who had spent months or years exposed to the high risk of infection in the European camps, with a short period of increased risk during the voyage to Australia. A clinical examination of children showed that malnutrition in the under five years group was fairly common. It was further noticed that about one child in six had a degree of cervical adenitis which was not accounted for by transient tonsillitis or pharyngitis, and a tuberculous ætiology was suspected. It suggested to us that one child in six, or 16%, of the nil to five years age group could be expected to give a positive Mantoux reaction. This would, of course, be a much higher figure than that found among Australian children in the same age group. Results obtained by some other workers are as follows: Adelaide (Fry), 15,000 children, 1·3%; Canberra (Pinner, 1950), 1134 children, 1·62%; Bendigo (Kerr, 1949), 6056 children, 1·0%; Sydney (Anderson, 1940), 6·0%.

We decided to get additional data on the tuberculosis picture among the displaced persons by conducting a Mantoux survey on the children up to the age of fifteen years. With the approval of the Director-General of Health a survey was conducted from March, 1950, to June, 1950, on the displaced persons migrant children in the centres at Bathurst, Cowra, Parkes, Uranquinty and Greta. The survey team carried its own apparatus and consisted of one Australian and two migrant doctors, speaking between them eight languages. Supplies of old tuberculin and B.C.G. vaccine were flown to the party from the Commonwealth Serum Laboratories, Melbourne.

On a voluntary basis 4721 children were tested; they represented 17% of all the displaced migrant children who had entered Australia up to the time when the survey was completed. Vaccination with B.C.G. vaccine was offered to all those who failed to react, and 1623 children were vaccinated.

Method of Mantoux Testing.

Old tuberculin, C strength (1: 1000 dilution), prepared by the Commonwealth Serum Laboratories, was used. One-tenth of a millilitre was injected intradermally into the

ventral surface of the left forearm and the resulting reaction was observed seventy-two hours later. At the beginning of the survey the arms were inspected at forty-eight hours and again at seventy-two hours. It was found, however, that while some children who had no reaction at forty-eight hours gave a frankly positive reaction at seventy-two hours, the reverse hardly ever occurred. Accordingly the forty-eight hour examinations were abandoned and the arms were inspected only at seventy-two hours after injection. The result was recorded as positive if an area of induration five millimetres or more in diameter was found by palpation with the index finger. The diameter in millimetres was recorded.

Method of B.C.G. Vaccination.

One-tenth of a millilitre of a recently prepared suspension was injected intradermally into the deltoid region of the left arm. The batch number was recorded. Some unpleasant complications of vaccination occurred, in the form of enlarged and fluctuant axillary glands. Among 499 children vaccinated in the Bathurst centre seven such cases occurred. In four the condition subsided with or without aspiration, but in three rupture through the skin occurred, leaving ragged craters which were slow to heal. The glandular enlargement was usually noticed eight weeks after the vaccination.

Some mothers stated that their children had been vaccinated with B.C.G. in Europe, and this statement was accepted if the typical scar was visible on shoulder or thigh. The World Health Organisation has lately supplied a yellow-covered booklet to register immunization injections, but in none of these booklets was B.C.G. vaccination recorded. A Danish mission conducted a Mantoux and B.C.G. survey in the displaced persons camps of Europe and a few of their brown cards were produced. We found that vaccination over the deltoid generally left a small, flat and inconspicuous scar, while on the thigh the scar was much larger and deeper.

In all, 1623 children were vaccinated by us, and it is hoped to carry out a control Mantoux test on as many of them as possible. No segregation after vaccination was practicable, and on this question we were guided by the views of Holm (McDougall, 1949):

> It should be stressed that when isolation is used at all, it is only to protect the reputation of the vaccine, and not because it is considered dangerous to give vaccine to a person in the so-called pre-allergic stage of a virulent tuberculous infection, nor especially dangerous for a person who is vaccinated to be exposed to a virulent tuberculous infection, before vaccination has made him a reactor to tuberculin. If vaccine is given to persons in the pre-allergic stage of a virulent tuberculous infection, the vaccination will, of course, have little or no value, and some cases of tuberculosis will develop. These cases do not develop because of the vaccination, but would develop in any case. Exactly the same is the case if newly vaccinated persons are exposed to virulent tuberculous infections. If it is possible to make segregation of the vaccinated persons in the tuberculous families, this, of course, should be done. However, the position is very often such that we either have to make a vaccination without segregation or to omit the vaccination. In this case we would prefer to make the vaccination without segregation, with the risk that some of the persons vaccinated would develop tuberculosis within a short period.

A remarkably high percentage of positive reactors was discovered, rising steadily from 3·9% at one year of age to 78% at fifteen years of age. The results are set out in graph form in Figure I and Table I.

A similar graph (Figure II) was constructed with the figures for males and females extracted separately (Table II), and this showed no significant sex difference up to the age of fifteen years. Subjects giving a history of previous B.C.G. vaccination were of course not used in the preparation of these figures. For purposes of comparison with Australian children of the same age the figures obtained by Kerr at Bendigo, Victoria, are superimposed on Figure I. It can be inferred from these graphs that practically no Europeans are reaching adult life without undergoing infection with Koch's bacillus.

The 4721 children tested fall into the following groups:

I: "Mantoux-positive" by natural infection .. 1438
II: "Mantoux-negative", not vaccinated 1188
III: "Mantoux-negative", vaccinated in Australia 1623
IV: Vaccinated in Europe—"Mantoux-positive" 247
V: Vaccinated in Europe—"Mantoux-negative" 225

TABLE I.

Positive Reactors (Not Vaccinated in Europe) in Percentages and Years.

Age. (Years.)	Total Positive Reactors.	Number Studied.	Percentage of Positive Reactors.
0	3	33	9·1
1	16	412	3·9
2	101	593	17·0
3	113	587	19·2
4	172	588	29·2
5	79	302	26·1
6	85	249	34·1
7	100	226	44·2
8	95	192	49·5
9	78	160	48·7
10	109	181	60·2
11	97	177	54·8
12	114	184	61·9
13	108	141	76·6
14	65	92	70·7
15	103	132	78·0
Total ..	1438	4249	

If endogenous infection is accepted as the main cause of adult respiratory tuberculosis amongst Europeans, then the numerous positive reactors in group I constitute a group of potential "breakdown" cases. Conditions in Australia are initially favourable for these subjects, as

TABLE II.

Percentage of Positive Reactors in Sexes and Years.

Age. (Years.)	Positive Reactors.		Non-Reactors.		Percentage of Male Reactors.	Percentage of Female Reactors.
	Male.	Female.	Male.	Female.		
0	2	1	14	16	12·5	5·9
1	7	9	205	191	3·3	4·5
2	60	41	255	239	19·0	14·7
3	64	49	235	239	21·4	17·0
4	102	70	201	215	33·6	24·6
5	42	37	112	111	27·3	25·0
6	45	40	96	68	31·9	37·0
7	53	47	67	59	44·2	44·3
8	46	49	47	50	49·5	49·5
9	49	29	46	36	51·6	44·6
10	56	53	38	34	59·6	60·9
11	49	48	45	35	52·1	57·8
12	53	61	33	37	61·6	62·2
13	54	54	20	13	72·9	80·7
14	31	34	14	13	68·8	72·3
15	51	52	13	16	79·7	76·5
Total	764	674	1441	1370	—	—

most spend a period of several months in the reception and holding centres, where there are healthy open-air existence and first-class nutrition. However, we have observed that on leaving the holding centres the families tend to condense in the great industrial areas. Apart from the change to an urban and often a slum environment, approaching adulthood, with the necessity to earn a living, child-bearing *et cetera*, will produce additional strains tending to cause endogenous infection. We have noticed the movement of New Australians to the industries which are the best paid, which are also those imposing heavy physical strain in day and night shifts. Many take advantage of the brevity of the forty-hour week to work at two jobs at once.

It is our hope that the whole group of displaced persons migrants will be followed up as closely as possible, in order to discover the breakdown cases as quickly as they occur. Such a follow-up should be possible, as the Commonwealth has complete records of the physical condition of all migrants on their entry into the country, and their

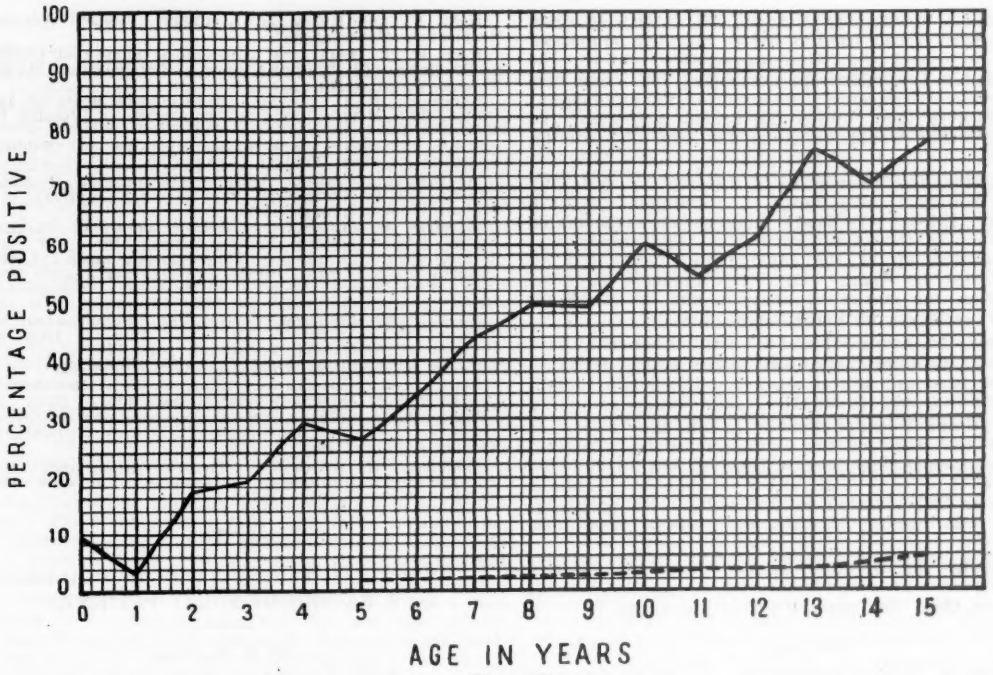

FIGURE I.

Positive reactors (not vaccinated in Europe), in percentages and years. Plain line, survey on "displaced person" children; interrupted line, survey of 6000 Victorian children (Kerr).

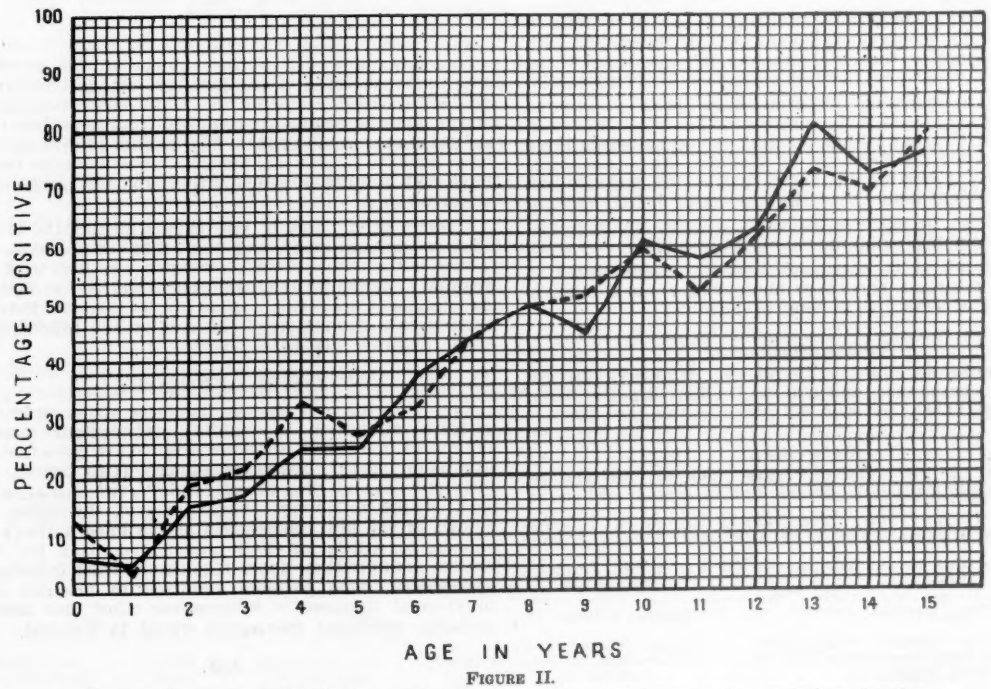

FIGURE II.

Percentage of positive reactors, in sexes and years. Interrupted line, males; plain line, females.

movements are guided by Commonwealth authority for the first two years. This seems to us to be an important aspect of the prevention of tuberculosis among the Australian population.

Efficacy of B.C.G. Vaccination.

Believing that the migrants would tend to live in groups together, we considered that the "Mantoux-negative" children ran a roughly European risk of infection at a later

date; in other words, they were almost certain to come in contact with Koch's bacillus before reaching adulthood. In order to protect the "Mantoux-negative" children as far as possible, the volunteers numbering 1623 were vaccinated with B.C.G. vaccine. The artificial immunity might at least protect them up to the school age when the natural infection would occur at the age of optimum resistance.

In assessing the efficacy of a vaccine by follow-up methods, Wallgren lays down the following criteria (McDougall, 1949). (i) There must be an unvaccinated control group of the same age and sex and standard of living, followed up at the same time. (ii) Risk of exposure must be equal. (iii) The numbers must be large enough for statistical analysis and to allow for individual variation in natural resistance.

In our opinion, groups II and III fulfil these conditions, and we hope to follow them up for many years. If B.C.G. vaccination is of any use at all, group III should show a lower morbidity than group II.

Groups IV and V are of interest, in that they give some return on the work of the Danish mission. The 472 children concerned had been vaccinated within the last two years, but 48% had either remained "Mantoux-negative" or had reverted to that state. No particular difference was noticed between the younger and older children.

Once again the question arises: Does the relative immunity persist after the tuberculin allergy has waned? If not, then these findings are rather depressing.

Summary.

1. A group of children representing 17% of all displaced persons migrant children brought to Australia up to June, 1950, has been Mantoux tested. With the mother's consent those failing to react have been given B.C.G. vaccine. A large percentage of positive reactors was discovered.

2. We accept endogenous infection as the main source of respiratory tuberculosis among European adults. We therefore consider the child reactors in this group to be a potential danger to themselves and to the community.

3. The non-reacting children have been vaccinated because of the social and economic future of their group.

4. A control group of non-reacting unvaccinated children which satisfies the demands of Wallgren has been established. By following up these groups we hope to get some additional data about the efficacy of B.C.G. vaccine.

5. We hope to perform an early control Mantoux test of the vaccinated children.

6. We think it is important that the whole group of European migrants should be supervised from a tuberculosis point of view for as long as possible.

Acknowledgements.

Our thanks are due to Dr. H. W. Wunderly for his advice and assistance, and also to Dr. Cerbuks, Dr. Soller and Dr. Barkauskiene, who did much of the hard work.

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MENINGEAL TUBERCULOSIS IN CHILDREN: A REVIEW OF FORTY PATIENTS.[1]

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THE patients who form the subject of this paper have been under the care of the members of the honorary and resident medical staffs of the Children's Hospital, Melbourne, and the results are compiled from in-patient records and follow-up examination. The results of treatment still leave much to be desired, though a great advance has been made with the use of streptomycin, and the prognosis now is not hopeless.

A series of 40 cases of tuberculous meningitis occurring between January, 1947, and July, 1950, is presented. The former is the date when streptomycin was first used at the hospital. Twenty-nine children received streptomycin therapy, of whom five appear to be cured. Before we proceed to a discussion of the results, the following diagnostic features will be considered.

Provisional Diagnoses.

The following provisional diagnoses were made on the patients' admission to hospital: tuberculous meningitis (13 cases), pyrexia of unknown origin (five cases), encephalitis (four cases), bronchopneumonia (two cases), meningitis (two cases), "for investigation" (two cases), and one each of the following: tuberculosis of the spine, tuberculosis of the hip, tuberculosis of the knee, miliary tuberculosis, tonsillitis, cerebral tumour, vomiting for investigation, malnutrition, upper respiratory tract infection, and septicæmia. The patients admitted to hospital with a provisional diagnosis of tuberculosis other than meningeal probably developed meningitis whilst in hospital.

Age.

There were 15 children under the age of two years, the youngest being aged five months at the time of admission to hospital. The remaining 25 were aged under fourteen years, and of these only two were aged over nine years.

[1] Read at a meeting of the Melbourne Pædiatric Society on September 13, 1950.

Excluded Cases.

Forty cases are considered, and for various reasons eleven are excluded from the streptomycin treatment series. Brief consideration of these excluded cases illustrates the diagnostic difficulties in this disease. In five cases the diagnosis was not made *ante mortem*, and brief details of these are as follows. (i) A six months' old infant had been an in-patient three weeks previously with meningococcal meningitis, and on readmission to hospital was thought to have a recrudescence of this condition. (ii) A child, aged two and a half years, lived for only nine days in hospital and had frequent convulsions; the Mantoux response was negative and the clinical diagnosis was cerebral abscess. (iii) An infant, aged eight months, had been in close contact with a patient with an "open" pulmonary tuberculous lesion; xanthochromic cerebro-spinal fluid was found on lumbar puncture, but clear cerebro-spinal fluid on ventricular puncture. A spinal block of uncertain ætiology was diagnosed, and tuberculosis was considered. (iv) One infant, aged ten months, lived for only three days in hospital, and was regarded as suffering from encephalitis, although the cerebro-spinal fluid sugar content was less than 10 milligrammes per 100 millilitres. (v) An infant, aged fourteen months, lived for only nine days in hospital, and was regarded as suffering from meningitis of uncertain ætiology. The cerebro-spinal fluid changes were compatible with tuberculous meningitis, and the Vollmer patch test gave a positive result. In four cases the diagnosis was established at the terminal stage of illness, the clinical details being as follows. (vi) A child, aged four years, was in a comatosed condition throughout her six days in hospital, and though a correct diagnosis was made, no treatment was given. (vii) A sibling, aged two and a half years, survived for only one week in hospital, and was at first considered to be suffering from post-vaccinal encephalitis, having had a previous history suggestive of vaccinia. (viii) One infant, aged five months, suffering from miliary tuberculosis, developed signs of tuberculous meningitis only one day prior to death. (ix) A child, aged five years, with tuberculosis of the hip and ankle joints, showed evidence of tuberculous meningitis one week prior to death. The remaining two patients excluded from the series received streptomycin by the intramuscular route only. (x) A five-year-old child, under treatment with streptomycin for tuberculosis of the lung and of the knee, showed signs of tuberculous meningitis a few days prior to death. (xi) A child, aged five years, with tuberculous meningitis secondary to spinal tuberculosis, at post-mortem examination was shown to have a tuberculous spinal abscess.

The remaining 29 patients have been studied to determine the value of the following aids to diagnosis: history of contact, positive Mantoux reaction, radiological evidence of pulmonary tuberculosis and characteristic cerebro-spinal fluid findings.

History of Contact.

A history of contact with a known sufferer from pulmonary tuberculosis was elicited in 15 of the 29 cases. Of interest is the fact that in only one of the excluded cases was such a history elicited.

Mantoux Response.

The response to the Mantoux test was positive in 24 cases, negative in three cases, and negative becoming positive under observation in one case. It was not recorded in one case.

Radiological Findings.

Abnormal pulmonary radiological findings were noted in 26 patients. They were normal in one case, and not recorded in two cases. The abnormality consisted of hilar gland enlargement in eleven cases, and miliary tuberculosis was evident in four. In the remainder, opacities were detected in the lung fields. It is worthy of note that of the four patients diagnosed as suffering from miliary tuberculosis by chest X-ray examination, two still survive. It is generally believed that there is an extremely poor prognosis when this condition coexists with meningeal tuberculosis.

Cerebro-Spinal Fluid Examination.

A summary of the details of the cerebro-spinal fluid findings on the patient's admission to hospital is given in Table I. A significant feature is the frequency with which a lowered sugar content is found. Although it is stated that a progressive fall in cerebro-spinal fluid chloride level is a reflection of the degree of vomiting (and this point is stressed in most recent publications on tuberculous meningitis), it seems from our results that a low chloride content is a strong indication of tuberculous meningitis. The figures for initial white cell counts indicate that a figure of 100 to 500 cells per cubic millimetre is by far the most common finding; figures considerably in excess of or below these do not exclude the diagnosis, the extremes in this series being 20 and 1300. With the exception of two cases, the cells were predominantly lymphocytes. The illness of one patient with chiefly polymorphonuclear leucocytes in the cerebro-spinal fluid ran an unusually fulminating course.

In few cases in this series were tubercle bacilli found in the centrifuged deposit of the cerebro-spinal fluid. A more successful result has recently been obtained by the method of MacFarlane, details of which were forwarded from England by Dr. John Perry. McFarlane advises that the cerebro-spinal fluid be centrifuged for thirty minutes at 3000 revolutions per minute, a drop of the deposit being placed on the glass slide and allowed to dry.

In all cases in this series the diagnosis was confirmed by the finding of tubercle bacilli in the cerebro-spinal fluid, by positive cultural findings in the cerebro-spinal fluid or by post-mortem examination.

Examination of the *fundus oculi* revealed chorioidal tubercles in several cases, but their detection was not recorded as a routine procedure. Recent experience has shown that the detection of chorioidal tubercles has been of considerable aid to early diagnosis.

Results of Treatment.

The average survival period of the patients who died was 112 days, ranging between twenty and 300 days. Twenty-nine patients have received prolonged streptomycin therapy. The disease is probably arrested in five patients who have normal cerebro-spinal fluid and no evidence of any sequelæ. There is no defect in any of the senses, the gait is normal, and all are alert mentally. Audiometry has been carried out and has failed to reveal any significant variation from normal in their hearing. The longest period during which any patient in this series has been under observation since

TABLE I.
Spinal Fluid Changes at First Examination.

Cells.		Sugar.		Chloride.		Protein.	
Number per Cubic Millimetre.	Number of Cases.	Milligrammes per 100 Millilitres.	Number of Cases.	Milligrammes per 100 Millilitres.	Number of Cases.	Milligrammes per 100 Millilitres.	Number of Cases.
20 to 50	3	Less than 10	19	600 to 650	12	50 to 100	6
51 to 100	6	10 to 20	1	651 to 700	13	101 to 200	16
101 to 500	16	21 to 30	3	701 to 760	4	201 to 400	6
502 to 1000	3	31 to 40	6			401 to 600	1
1000	1						

the cessation of treatment is thirty-two months, while the shortest period is nine months. The condition of the additional four survivors is as follows. (i) One patient, off all treatment for three weeks, remains well, and has normal spinal fluid findings. It is eight months since the disease was diagnosed. (ii) One patient, recently off all treatment twenty-one months after diagnosis, has normal cerebro-spinal fluid, but presents some evidence of sequelæ —namely, a slight limp and impaired hearing in one ear. However, his gait is rapidly improving. (iii) One patient, still on maintenance intramuscular streptomycin therapy after twelve months' treatment, though a little ataxic, is rapidly improving. His cerebro-spinal fluid is normal. (iv) The fourth patient, a child who was aged only fifteen months on admission to hospital and who had radiographic evidence of miliary tuberculosis, has recently relapsed after nine months' therapy.

After what appeared to be an adequate course of treatment, relapse occurred in five patients, three of whom are in the apparently "arrested" group, and two have died.

Hence the presumptive number of cures out of 29 treated patients is at a minimum five and at a maximum nine.

For comparison the following reports from overseas may be quoted (Table II).

Prognosis.

This series confirms many published reports that the prognosis is usually poor for a patient aged less than two years. The only survivor from this group has recently relapsed. The prognosis varies with the stage of the disease at the time of diagnosis. The earlier treatment is commenced, the better prospect there is that the disease may become arrested. To illustrate this point, these cases have been divided into three groups as follows. (i) The first stage is characterized by non-specific symptoms such as fever, malaise, irritability, anorexia, loss of weight, headache and vomiting. Eight surviving patients were in this group. (ii) In the second stage neurological signs first appear. Drowsiness becomes a noticeable feature, while cranial nerve palsies and spasticity are evident. One surviving patient was in this group. (iii) In the third stage of coma, there were no survivals. Many patients were examined for the first time in the later stages; this stresses the need for earlier diagnosis now that it is possible to arrest the disease process. The presence of coma is not in itself a contraindication to treatment, for one child admitted to hospital in a drowsy condition passed into a comatosed state which lasted for some weeks, and now shows indications of recovery.

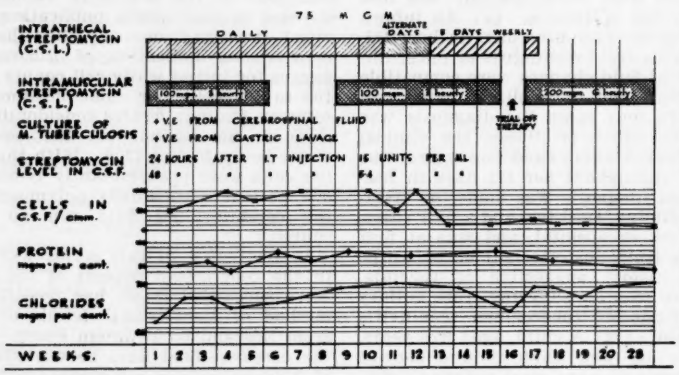

FIGURE I.

Details of treatment of E.K., aged eight years, in 1947. This child has probably completely recovered.

The number of patients in this series with coexistent miliary tuberculosis is too small to have much significance. However, to point to the fallibility of these generalizations as applied to an individual case, the following may be cited.

A relatively young patient, aged two years and three months, had miliary tuberculosis, and her condition was diagnosed late (second stage). She had a cranial nerve palsy, and retrogressed after a period of initial improvement, but has now apparently recovered.

Treatment.

"It is now widely believed that treatment with streptomycin is mandatory in early cases of miliary tuberculosis and tuberculous meningitis."

Since January, 1947, every endeavour has been made to treat all patients suffering from tuberculous meningitis with streptomycin, and the result has justified this form of treatment, and also the above view expressed by the American Trudeau Society (Riggins and Hinshaw, 1947).

The most favourable results will be obtained when the diagnosis is made early, and it has already been explained that this is not always easy. Tuberculous meningitis may be suspected when a child or infant who has been in contact with a known subject of pulmonary tuberculosis develops an illness suggestive of meningitis. Frequently the onset is by vague signs of meningitis with headache, vomiting and fever, and the routine lumbar puncture and cerebro-spinal fluid examination in such cases reveals an increase in lymphocytes, a chloride content below 700 milligrammes *per centum*, and a sugar content below 20 milligrammes *per centum*. Examination of a smear from the centrifuged deposit in the cerebro-spinal fluid may reveal tubercle bacilli.

In the cases reported a definite diagnosis was possible three or four weeks later when tubercle bacilli were grown in culture from the cerebro-spinal fluid by Dr. Reginald Webster. In one fatal case the cultural finding from the cerebro-spinal fluid obtained *ante mortem* was negative, and tubercles were found at post-mortem examination.

Treatment with streptomycin must not be delayed until the results of culture of the cerebro-spinal fluid are available.

A positive response to the Mantoux test and signs of meningitis, though strong presumptive evidence of active tuberculous meningitis, are not always an indication for streptomycin therapy, for two patients not included in this series had a mild cerebral reaction at the time when a

TABLE II.

Authority.	Place.	Date.	Number of Cases.	Number of Recoveries.	Recovery Rate.
Medical Research Council	England.	April, 1948.	105	30	28% (good progress after 120 days).
Cairns and Taylor..	Oxford.	January, 1949.	48	28	58%
Choremis	Athens.	October, 1948.	50	21	42%
Russell and MacArthur	Glasgow.	January, 1950.	33	10 (5 disabled)	30% *plus* 15% disabled.
McCarthy and Mann	London.	February, 1950.	37	14	38%
Veterans' Administration.. ..	United States of America.	March, 1950.	66	Not published	33%
Lincoln and Kirmse	New York.	April, 1950.	21	16	76%
Honor Smith and Vollum	Oxford.	August, 1950.	42	20	48%

positive Mantoux reaction was first detected. Lymphocytes up to 80 per cubic millimetre were found in the cerebro-spinal fluid, yet the patients' malady lasted only seven days, and they made a complete recovery without any special therapy.

Before intrathecal streptomycin therapy is begun, every endeavour must be made to arrive at a correct diagnosis, and a culture of the cerebro-spinal fluid commenced. If possible, guinea-pig inoculation should also be carried out. The reaction due to intrathecal streptomycin therapy makes it impossible to reassess the case adequately. In doing this, delay in treatment is to be avoided.

From the commencement of treatment full cooperation with the neurosurgeon is most desirable, and we have been fortunate in the help received from Dr. Reginald Hooper. Seven of these patients had intraventricular injections of streptomycin.

Treatment with Streptomycin.

Intramuscular injections of 50 to 100 milligrammes of streptomycin were given at three-hourly intervals, and intrathecal therapy consisted in the administration of 25 to 100 milligrammes in two to five millilitres of saline or distilled water at first by daily injection.

In view of the results of assay of the streptomycin content in the cerebro-spinal fluid after twenty-four and forty-eight hours, it was considered that daily intrathecal

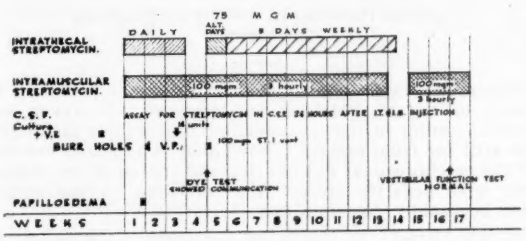

FIGURE II.

Details of treatment of L.M., aged seven years, in 1947. This child has probably completely recovered. Streptomycin is now given intramuscularly once or twice a day after the first two weeks.

injections were perhaps unnecessary, but that injections on alternate days were too infrequent. Accordingly, the routine has been to give intrathecal injections on five days per week, omitting the injection on Wednesday and Sunday, after an initial two weeks of daily injection. After two weeks it is best to give intramuscular injections once or twice daily.

If a block in the flow of cerebro-spinal fluid was observed (detected by the presence of xanthochromic fluid with a rise in protein content, by a persistently poor flow through the lumbar puncture needle, and by a negative response to the Queckenstedt test), streptomycin was given by ventricular puncture with the assistance of the neurosurgeon.

Information as to the degree and site of the block in the flow of cerebro-spinal fluid was sometimes obtained by cisternal puncture, but streptomycin was not given by that route. The injection of air may be used to determine the site of the spinal block.

Period of Treatment.—In three successful cases with the longest period of observation, intrathecal therapy was continued for periods of ninety-nine, 120 and 140 days, whilst intramuscular injections were carried out over periods of 137, 172 and 184 days. On occasions in 1947, streptomycin was not available and treatment was suspended for periods up to two weeks, and at other times, because of a reaction due to streptomycin, intrathecal therapy was stopped for several days for the examination of the cerebro-spinal fluid, particularly for cells, protein, sugar and chloride. If the fluid had returned to normal or approached normal and the disease appeared to be arrested, no further intrathecal therapy was used. When intrathecal injections were stopped, intramuscular therapy was continued for a period up to twelve months, during which time repeated lumbar punctures were performed, the fluid was examined and the whole clinical picture was assessed for indication of cure.

Toxic Effects.—A painful reaction lasting a few seconds to a minute was usual after the intramuscular injections. Late in the period of treatment in the earlier cases, and in all recent cases, injections were given at six-hourly intervals, then at twelve-hourly intervals or once a day. The intrathecal injection is also painful, and occasionally a slight syncopal effect was seen—this was never serious enough to stop treatment; similarly, with intraventricular injections. Perhaps our experience is more fortunate than that of others, but the usual disturbance of balance and hearing connected with prolonged streptomycin therapy has not been evident in our cases.

Ancillary Treatment to Streptomycin.

1. Streptokinase is the fibrinolytic enzyme obtained from cultures of certain strains of hæmolytic streptococci, and in view of a report of its use by Cathie, supplies were prepared at the Commonwealth Serum Laboratories. No toxic effect is associated with the injection of streptokinase intrathecally, and it is given over a period of six weeks; at the same time streptomycin is given intrathecally. There have been no confirmatory reports from overseas of the value of streptokinase, and my opinion is that it is worthy of further trial. In the Children's Hospital, Melbourne, it has been used in the last seven cases, in two of which promising improvement has been detected. More details of streptokinase therapy have already been published in this journal (Williams and Bazeley, 1950).

2. Para-aminosalicylic acid (Lehmann, 1946) given by mouth is now used, in a dose of three to five grammes daily for a child. For larger children the adult dosage of 10 to 12 grammes daily can be given. It is administered in the form of a mixture, and sometimes as granules sprinkled on cereals or sandwiches. Both the sodium and potassium salts are used to prevent electrolytic disturbance. There is good evidence that this drug has a "detoxifying" action on the tubercle bacillus and inhibits the production of streptomycin resistance. In one fatal case in which streptomycin was used without para-aminosalicylic acid, a resistant strain of *Mycobacterium tuberculosis* developed. In two fatal cases the organism isolated at post-mortem examination remained sensitive. Cathie had a similar experience, and it is generally accepted that the development of streptomycin resistance is not the chief cause of failure in fatal cases of meningeal tuberculosis.

Para-aminosalicylic acid passes the blood-brain barrier into the cerebro-spinal fluid in a concentration of one-quarter to one-third of that in the blood in meningitis when given by mouth.

Honor Smith and Vollum (1950) have published details of the use of purified protein derivative of tuberculin given by intrathecal injection. In a most searching inquiry into the differences between successful and fatal cases it has been shown that the reaction in the cerebro-spinal fluid as indicated by a rise in the number of cells and an increase in the protein content is less pronounced in fatal cases. By the injection of varying amounts of a solution of 7·5 microgamma of purified protein derivative per millilitre diluted 10-fold, 100-fold and 1000-fold, a reaction is obtained.

This treatment is in use in four cases, two of the children concerned being included in the above series. It is very much in the experimental stage, and present indications are that it is best reserved for patients who are not responding to streptomycin treatment alone.

Summary.

Twenty-nine patients suffering from tuberculous meningitis have been treated with streptomycin at the Children's Hospital, Melbourne, between January, 1947, and July, 1950. In five the disease has probably been arrested, and an additional four have a reasonable chance of recovery. The mortality is between 70% and 80%.

Early diagnosis offers the best chances for recovery. In tuberculous meningitis, this is possible by the performance of a lumbar puncture on children with minor cerebral symptoms who have a history of contact with adult patients suffering from pulmonary tuberculosis. This contact requires searching interrogation. The Mantoux test produced a positive reaction in 82% of patients.

The cerebro-spinal fluid change on the first lumbar puncture consists typically of an increase in cells to between 100 and 500 per cubic millimetre. The cells are chiefly lymphocytes. A fall in cerebro-spinal fluid sugar content below 10 milligrammes *per centum* is usual. The cerebro-spinal fluid chloride level was below 700 milligrammes *per centum* in 86% of patients.

There were no survivors amongst the group of children admitted to hospital in a comatosed condition. Eight of the other children who survived had vague symptoms of malaise, irritability, anorexia, loss of weight, headache and vomiting without abnormal neurological signs on their admission to hospital.

Treatment advised is by intramuscular injections of streptomycin, 50 to 100 milligrammes, three-hourly for one week, then twice the dose six-hourly for one week. For the remainder of the period of treatment the daily dose of half a gramme to one gramme can be given in two daily injections. This is continued for at least six months. Intrathecal streptomycin therapy is required daily for two weeks, then five days per week for at least two months. The dose is 25 to 100 milligrammes dissolved in two to five millilitres of saline or distilled water. Three patients who are apparently cured and have been observed for more than two years had intrathecal streptomycin therapy for ninety-nine, 120 and 140 days respectively.

The administration of para-aminosalicylic acid by mouth is advised in a dose of three to ten grammes daily.

There have been no toxic effects from the use of the fibrinolytic enzyme streptokinase used intrathecally at the same time as the injection of streptomycin in seven patients who were used to test this treatment. The results do not warrant its being used as a routine procedure and streptokinase remains under investigation.

Purified protein derivative of tuberculin is under investigation. The indication for its use appears to be absence of response to intrathecal and intramuscular streptomycin therapy alone.

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Full appreciation goes to the resident medical officers of the Children's Hospital, Melbourne, for their skilful ministrations to the patients. For the early supplies of streptomycin and for considerable technical advice, our thanks are due to the Director of the Commonwealth Serum Laboratories, Melbourne, and the members of his staff, Dr. E. V. Keogh and Dr. John Funder. The cooperation of the members of the staff of the Children's Hospital has been much appreciated, and we thank Dr. H. Boyd Graham, Dr. R. Southby, Dr. M. L. Powell, Dr. Vernon Collins and Dr. Howard Williams for permission to publish the results of treatment of patients under their care. Dr. E. Graeme Robertson, consultant neurologist, has given much helpful advice. Dr. Reginald Webster and Dr. John Perry have guided us in the laboratory investigations, and we thank also Miss Shirley Fenton and Miss Janet McLaren for their technical help. Dr. Alan Williams's paper on the pathology of tuberculous meningitis was prepared by him from material associated with this investigation. His findings and advice have been of considerable value to the clinicians.

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PATHOLOGY OF TUBERCULOUS MENINGITIS, WITH PARTICULAR REFERENCE TO MODIFICATION IN PATHOLOGY FOLLOWING TREATMENT WITH STREPTOMYCIN.[1]

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STREPTOMYCIN is without doubt a substance potent in its action on the *Mycobacterium tuberculosis*. However, successful results in the treatment of tuberculous meningitis are still far from assured. Even though repeated cultures of the cerebro-spinal fluid during the course of the disease may give negative results, the condition of the patient may be rapidly deteriorating.

In an attempt to determine the reasons for failure to obtain a clinical cure in a disease in which we have an apparent bacteriological cure, the nature of the lesions present in the central nervous system must be examined.

In this paper will be discussed the development and nature of two lesions frequently found at post-mortem examination—namely, hydrocephalus and ischæmic changes in the brain. It is not proposed to discuss the incidence of meningitis in tuberculosis, the origin and spread of the meningeal lesion, or the lesions of other viscera present at necropsy.

The tissue changes which occur in an inflammatory reaction are dynamic in their nature, and in histological sections prepared from biopsy or autopsy material is seen a picture of a process which has been halted either artificially or by the death of the patient. As the process is a changing one, different pictures will be present should the lesion be examined at different times. This change in the picture with the passage of time must be stressed, as it is a major factor in variations in the picture of tuberculous meningitis as seen by a morbid anatomist.

The tissue response to damage caused by the *Mycobacterium tuberculosis* follows the general pattern of inflammation. Evidence is present of the occurrence of cell damage, of early tissue responses and of the reactions that occur later. Nowhere have we better opportunity to see the early response than in the meningeal lesions. It is reflected in the changes that occur in the cerebro-spinal fluid—a cellular response resulting in an increased cell count, which in the early stage of the disease may consist mainly of an increase in polymorphonuclear cells and a vascular reaction which results in an increased cerebro-spinal fluid pressure and protein content. We do not frequently have such an opportunity to study the early inflammatory response following the lodging of the tubercle bacillus in lung or in bone. It is more common to see

[1] Read at a meeting of the Melbourne Pædiatric Society on September 13, 1950.

there the picture of a process which has been active for some time; and even in rapidly developing miliary tuberculosis the lesion is usually weeks old at the time of autopsy and the histological picture has changed. The prominent cells are now mononuclear in nature, as they are in meningitis of similar duration. Moreover, in lesions —whether pulmonary, glandular, of joint or of bowel— which have been present for some months is seen the late tissue response—a multiplication of fibroblasts with the production of at first vascular and cellular granulation tissue, but then later of dense collagenous connective tissue.

It is thus that a change is now apparent in specimens from autopsies performed on children who have suffered from tuberculous meningitis, for whereas the development of the pathological process was formerly stopped by the death of the child within six weeks of the commencement of the illness, now the child may remain alive for months or years.

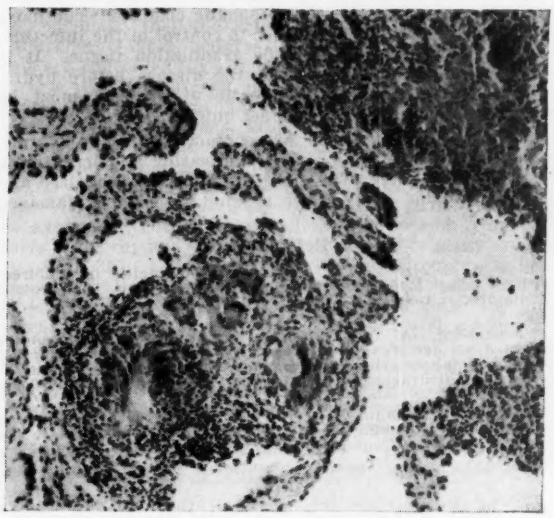

FIGURE I.
Chorioid plexus, with well-developed giant-cell systems, from a case of tuberculous meningitis (×120 approximately).

Before I describe the autopsy findings that are seen in those children whose life has been lengthened by the use of streptomycin, mention will be made of the intracranial findings in the untreated subject.

Prior to the advent of streptomycin, the course downhill was relatively rapid, the death of the patient occurring in one to six weeks. At autopsy the presence of meningitis was obvious. This process often appeared macroscopically to be localized to the base of the brain, and limited perhaps to the interpeduncular space and the area around it. In cases of longer duration a more extensive exudate was present, often extending over pons, medulla and cerebellum, and forwards between the cerebral hemispheres and over the *corpus callosum*. Ultimately the meninges over the vertex were involved. The exudate in the early cases was just slightly opaque and turbid, a change in the later ones to a greenish-yellow colour being apparent. Minute tubercles, often detected only on examination with a hand lens, could be seen—usually along the course of the meningeal vessels. Dilatation of the ventricles was usually not appreciable, and a gross degree of hydrocephalus was a rarity rather than the commonplace finding that it is today.

Lincoln (1947), reporting a series of 167 cases of untreated tuberculous meningitis, states that in autopsies in 40 cases of duration of less than three weeks, slight dilatation of the ventricle was observed on nine occasions; whereas in autopsies in 22 cases of duration greater than three weeks, slight dilatation of the ventricle was observed on 11 occasions and pronounced dilatation on three occasions.

Shonenberg (1950), reporting on a series of 26 children suffering from tuberculous meningitis, examined encephalographically prior to the institution of streptomycin therapy, noted pronounced dilatation of the ventricle in three cases only, although he states that it was noticeable in all the others.

In the 12 subjects which have come to autopsy after streptomycin treatment, the duration of the disease has varied from one to eight months. In all cases the presence of meningitis was evident, the greatest collection of exudate being situated at the base of the brain, in the region of the interpeduncular fossa. The thickened nature of the meninges, both in this region and surrounding the spinal cord, was evident, and in these thickened meninges, which were composed of tuberculous granulation tissue, were situated well-formed tubercles with a diameter up to

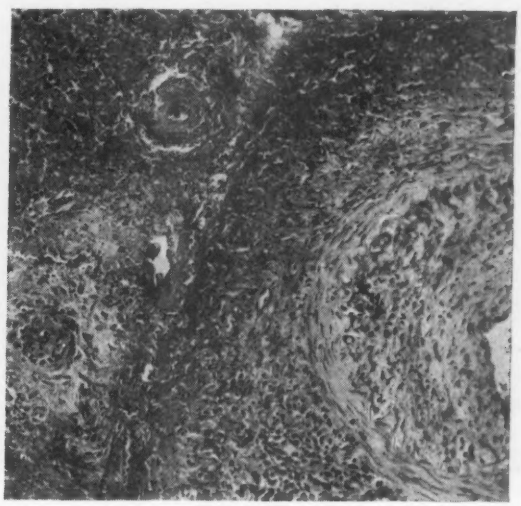

FIGURE II.
Intimal thickening in meningeal vessels in tuberculous meningitis (×120 approximately).

0·5 centimetre. The majority of nodules were not so large as this, but they were nevertheless visible with extreme ease.

This accumulation of granulation tissue was most intense in the interpeduncular space and the proximal part of the Sylvian fissure, but could be traced along the course of other vessels leaving the circle of Willis. These arteries were usually embedded in the exudate, and changes in their walls accompanied sometimes by thrombosis have been noted.

The presence of hydrocephalus has been a constant feature. The gross dilatation of the entire ventricular system could be explained by obstruction to the flow of cerebro-spinal fluid in various sites. At autopsy it is difficult to be sure of the actual site of obstruction. Honor Smith and fellow workers (1948) state that the hydrocephalus (which is communicating in type) present in their cases was due to obstruction in the interpeduncular fossa, together with a varying degree of obstruction in the tentorial opening. They suggest that upward displacement of the vermis of the cerebellum may occur to complete the obstruction. Findings at our own necropsies could be compatible with this theory, for which the Radcliffe Infirmary workers have the supporting evidence of X-ray studies, after air injections into the subarachnoid space during life, which showed arrest of the bubble of air in the interpeduncular fossa, sometimes for days. As symp-

toms of acute hydrocephalus are rare, the obstruction to the passage of cerebro-spinal fluid over the cerebral hemispheres is certainly not absolute.

However, acute hydrocephalic episodes have been reported, and these are due possibly to total obstruction by upward displacement of the cerebellum. These episodes may be temporary or terminal.

Another possible site of partial obstruction is at the foraminæ of Luschka and of Magendie. At one autopsy, in which dilatation of the entire ventricular system was found to be pronounced, a considerable amount of exudate was present in the fourth ventricle. In this child numerous well-formed tubercles were demonstrated in the chorioid plexus (Figure I) and the ventricular walls were thickly covered in many places by exudate. However, autopsy studies such as these can suggest rather than prove the site of obstruction, and further experiments of the air-bubble type seem indicated.

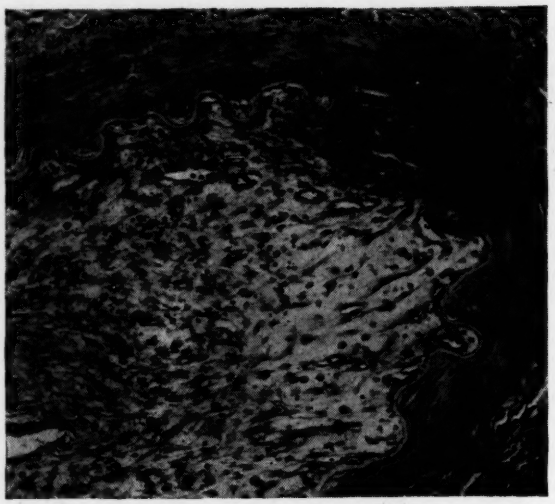

FIGURE III.

Subintimal proliferation of fibroblasts, with revascularization occurring (× 300 approximately).

Another lesion which must be mentioned is the inflammatory reaction in the spinal meninges. Here both the macroscopic picture with its dense fibrous tissue and macroscopic tubercles, and the microscopic picture, are identical with those of the cranial meninges. The space-occupying nature of this lesion, *plus* involvement of all meningeal layers, is sufficient to account for the signs of spinal block which unfortunately occur—complicating an already difficult therapeutic regime.

In the description of the exudate around the base of the brain, mention was made of the fact that changes in vessel walls were observed. This finding was not limited to subjects who had been treated with streptomycin.

Periarteritis, endarteritis and thrombosis have been noted frequently in untreated subjects. Examination of the walls of the smaller vessels revealed acute inflammation and even necrosis. The subendothelial œdema and cell infiltration, sometimes with the addition of thrombosis, produced severe diminution of the lumen, and ischæmic lesions of brain of recent nature were found *post mortem*.

With the prolongation of the disease process, lesions of more chronic nature are now seen—both in small arteries and in larger calibre vessels. The most common finding is a proliferation of subendothelial fibroblasts. Virtual obliteration of the arteries has been observed—they have scarcely been recognizable as vessels (Figures II and III).

Accompanying these vascular changes have been lesions of the brain. These have varied in their appearance from softening of the cerebral tissue to actual cyst formation. The areas involved vary, but the basal ganglia are the most common site, although other areas include temporal poles, mid-brain and hypothalamus.

Conclusion.

In conclusion, I should like to express the following viewpoints.

1. Streptomycin has changed the course of the disease that we are discussing from one of acute to one of chronic nature, and in the morbid anatomical findings are featured prominently those tissue changes which we associate with chronic tuberculosis—namely, caseation and fibrosis.

2. Streptomycin therapy has often enabled us to render the cerebro-spinal fluid of a patient sterile, but that patient has died—for mechanical reasons. The drug has not prevented the slow response to tissue damage caused by the *Mycobacterium tuberculosis*, and the forming granulation or scar tissue has, by its occurrence in certain sites, been the cause of progressive hydrocephalic changes. The more extensive the damage done prior to control of the infection, the more extensive will be the granulation tissue. It is obvious that if we are to cure the disease before hydrocephalus develops, the therapeutic agent used must be administered early, and must act quickly.

3. Vascular changes are widespread, and being progressively occlusive in nature cause increasing and irreparable loss of brain tissue. The condition must be recognized and patients treated early if we are not to leave a damaged brain.

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SOME EXPERIENCES IN THE USE OF THE ADRENALINE TEST IN 51 CASES OF RHEUMATOID ARTHRITIS.

By L. J. A. PARR, EVA A. SHIPTON, AND PAUL WHITE,

Sydney.

MANY of the earlier observations on the effect of adrenaline on the blood picture are confusing. Kagi (1920) critically reviewed the subject. Patek and Deland (1935) review the findings reported in the literature on the effect of adrenaline on the blood and also the causes of the increase in the number of white cells, and add blood studies on two normal persons after a single subcutaneous injection of adrenaline. A review is also made of nine patients with hæmolytic jaundice, four of them after splenectomy, and on five patients with splenomegaly from various causes. In all cases leucocytosis involving both myeloid and lymphoid cells occurred in the first two hours. In the two normal subjects the lymphocyte count (at the end of three and a half to four hours) was lower than in the count before the adrenaline was given. In three of the four patients who had undergone splenectomy this was noticeable, but in one the lymphocyte count rose from 4400 to 7600 per cubic millimetre at the end of four hours. The number of eosinophile cells was not recorded in any case. The authors conclude that, since the changes observed were not greater in patients with spleens than in those after splenectomy, they appear not to be due to splenic contraction, and they suggest that a mechanical alteration

the blood-stream involving many areas and organs in the body is responsible for the effects observed. Lucia *et alii* (1937) studied the effects of adrenaline stimulation on the leucocyte counts of 33 patients, seven of whom had undergone splenectomy, taking the counts ten, twenty, forty, sixty and 100 minutes after the injection of one millilitre of adrenaline (one in 1000).

In all the patients leucocytosis existed, and examination of the blood of patients who had undergone splenectomy revealed a leucocytic response which differed little from that of those patients whose spleens had not been removed. The lymphocytes increased earlier and to a relatively greater degree than the other cellular elements. No mention is made of the eosinophile cell counts. A tendency to a secondary rise in the neutrophile cells was noted. Five possible causes for the changes in the leucocyte count after the injection of adrenaline are discussed—namely, splenic contracture, hæmoconcentration, direct stimulation of the bone marrow, redistribution of the formed elements of the blood and expulsion of leucocytes from the lymph nodes. These specialists consider that the results do not warrant the conclusion that the bone marrow is stimulated; but Walterhofer (1921) believes that if the adrenaline injections are continued for a long time hyperplasia of the bone marrow results. Interest in the changes in the leucocyte count in the peripheral blood after the subcutaneous injection of adrenaline has been greatly stimulated since Dougherty and White (1944) showed that the administration of the adrenocorticotrophic hormone of the anterior pituitary lobe caused lymphopenia and the destruction of lymphoid tissue. That some relationship exists between the suprarenal cortex and the lymphocytes and lymphoid tissue and thymus has been believed for many years (Bergel, 1921). Until the present time much confusion has existed as to the exact relationship. Catel and Jedas (1930) found a disappearance of the eosinophile cells and an increase in the lymphocytes after treatment with a preparation made from the suprarenal cortex.

Dalton and Selye (1939) showed that "the so-called non-specific leukocytosis preceded by a decrease and followed by an increase in eosinophils is a constant feature of the alarm reaction". Selye has also shown (1946) that the lymphocytopenia resulting from adrenal cortical stimulation is part of the reaction to stress in the adaptation syndrome.

Long and Fry (1945) showed that the injection of pure adrenotrophic hormone into rats was followed by a rapid fall in adrenal ascorbic acid content, a slower fall in adrenal cholesterol content and an increase in liver glycogen content. Experimenting on rats, they then showed that epinephrine (adrenaline) administered subcutaneously or intravenously caused an unmistakable fall in adrenal cholesterol and ascorbic acid content, and that this effect was abolished by hypophysectomy.

Vogt (1944) showed that intravenous infusion of adrenaline in the eviscerated dog or cat caused a strong immediate and long-lasting stimulation of suprarenal activity. She obtained this effect with doses of adrenaline which occur in the body under physiological conditions, and the action was independent of the blood flow and blood pressure and not mediated by a hormone from the pituitary. She concludes that through adrenaline the sympathetic nervous system has indirect control over the activity of the suprarenal cortex. In 1945, Vogt, using prolonged adrenaline injections in normal and hypophysectomized animals, obtained results which seemed to indicate that adrenaline stimulates the anterior pituitary lobe to secrete ACTH.

Long (1947) believes that there are three possible paths through which epinephrine may act to cause a release of corticosteroids: (i) by direct action on the pituitary gland, causing a release of ACTH, which acts upon the adrenal cortex; (ii) by producing a drop in the level of cortical hormone in the blood, which in turn produces an increased release of ACTH by the pituitary; (iii) by direct action on the adrenal cortex, causing a release of the cortical hormone.

Speirs and Meyer (1949), using eosinophile cell counts in mice, confirmed the belief that the main action of adrenaline is on the pituitary but that there may be some direct action on the suprarenal cortex. They found that removal of the adrenal cortex prevented the eosinopenia due to stress and epinephrine, and that instead slight eosinophilia occurred. Injection of adrenaline in man is at present assumed to cause some ACTH production by the anterior pituitary lobe, which results in the production of corticosteroids, and of polymorphonuclear leucocytosis, lymphocytopenia and eosinopenia in the peripheral blood. This assumption has been strengthened by some recent work of Samuels *et alii* (1950), who found that epinephrine, and to a lesser extent nor-epinephrine, in 20 human subjects caused a significant primary response with increase of neutrophile cells, lymphocytes and eosinophile cells with a maximum effect at fifteen minutes after the injection, the figures returning to normal within one hour. This primary neutrophile cell rise appears to be influenced by the absence of the spleen, being absent in patients subjected to splenectomy. The secondary change commenced about the end of the first hour, reached a maximum response within two to four hours, and was characterized by a rise in the total numbers of leucocytes and neutrophile cells and a fall in the numbers of lymphocytes and eosinophile cells. Adrenergic blocking agents were incapable of altering this secondary response. The authors conclude that the primary response appears to be concerned with complex circulatory adjustments and the secondary response with stimulation of the hypothalamic-pituitary adrenal system. Dury (1950) has also shown that absence of the spleen prevents the typical response of the lymphocytes and neutrophile cells to adrenaline injection.

Godlowski in 1948 called attention to the eosinopenia following adrenaline infusion and insulin therapy, as did Laragh and Almy in the same year. It has long been the practice of one of us to treat certain types of rheumatoid arthritis especially associated with vasoconstriction and loss of weight with insulin, and febrile rheumatoid patients with adrenaline. Godlowski (1949) has also recently brought this method of treatment to the front.

The Present Investigation.

During the treatment of many patients a few will be found who fail to respond to the treatment, and it was this fact that stimulated the following work in an attempt to decide which patients would respond and which would not. With a few minor modifications the method of Thorn (1949) was used for the test. The patient was kept fasting for twelve hours, and an eosinophile cell count was made by the direct method of Dunger (1910) and also indirectly from the usual method of making white-cell counts and differential counts, 200 white cells being counted in the differential count. The modification of Jackson (1950) was found of great help, as with it there is no need to count the cells immediately. Adrenaline hydrochloride 0·5 millilitre (Parke, Davis) was injected subcutaneously, and material for eosinophile cell counts, total leucocyte counts and the preparation of slides was collected at intervals of one, two, three and four hours. Nearly all the patients suffered a reaction after the adrenaline.

The following list comprises patients examined in two public hospitals and in private practice. Some degree of difference in the extent of the tests is revealed in the table, and it is obvious that the full test is time-consuming. However, the full test from the point of view of experimental clinical research is extremely valuable, the numbers of total leucocytes, neutrophile cells, lymphocytes and eosinophile cells giving a complete picture. All the private patients had the full test.

In this series were seven subjects who failed to respond in the typical fashion to adrenaline; this would indicate some abnormality in the hypothalamic, pituitary, adrenal-cortex system.

In one case the test result was labelled as being doubtful as there were no eosinophile cells present in the blood slide and therefore no estimate was made before adrenaline was given. However, after the first hour the number counted was estimated as 120, but none were present in the slides at the end of the second, third and fourth hours.

TABLE I.
Adrenaline Tests.

Case Number.	Patient's Sex.	Total Leucocytes.[1]	Neutrophile Cells.	Lymphocytes.	Eosinophile Cells.	Result.	Erythrocyte Sedimentation Rate.[3]	Type of Illness and Duration.
1	F.	+	+	−	−50%	Positive.		
2	F.	+	+	−	−50%	Positive.	62	Chronic, 15 years.
3	F.	+	+	−	−50%	Positive.	30	Chronic, 10 years.
4	F.	+	+	−	−50%	Positive.	6	Chronic, 9 years.
5	F.	+	+	−	−50%	Positive.	5	Chronic.
6	M.	+	+	−	−50%	Positive.	35	Chronic, 5 years.
7	F.	+	+	−	−50%	Positive.	26	Chronic, 1 year.
8	M.	+	+	+	−50%	Positive.	66	Chronic, 18 months.
9	F.	+	+	−	−50%	Positive.	46	Chronic, 3 years.
10	F.	+	+	+	−50%	Positive.	48	Chronic, 15 years.
11	F.	+	+	−		Doubtful.[2]	65	Chronic, 2 years.
12	M.	+	+	−	+	Negative.	74	9 months' history.
13	M.	+	+	+	−50%	Positive.	76	Chronic, 5 years.
14	F.	+	+	−	−50%	Positive.	13	Chronic, 7 years.
15	F.	+	+	−	−50%	Positive.	18	Chronic, 2 years.
16	F.	+	+	−	−50%	Positive.	16	Chronic, 9 months.
17	F.	+	+	−	−50%	Positive.	50	Chronic.
18	F.	+	+	−	−50%	Positive.	13	Chronic, 2 years.
19	M.	+	+	−	−50%	Positive.	29	Chronic, 6 years.
20	F.	+	+	−	−50%	Positive.	5	2 months.
21	M.	+			−50%	Positive.	14	Chronic, 1 year.
22	F.	+	+	−	−50%	Positive.	15	Chronic, 6 months.
23	F.	+	+	−	−40%	Negative.	74	Acute.
24	F.	+	−	−	+	Negative.	18	Chronic.
25	F.	+	+	+	−	Positive.	75	Chronic, Still's disease.
26	F.	+	+	−	−50%	Positive.	48	Chronic, bedridden for years.
Repeated 11 days later		+	+	+	+	Negative.	48	Chronic, bedridden for years.
27	F.	−	+	−	+	Negative.	132	Chronic, invalid, bedridden.
28	F.	+	+	−	−50%	Positive.		Early.
29	F.	−	−	−	−50%	Positive.	43	Chronic.
30	F.	+	−	+	−50%	Positive.	24	Chronic.
31	M.	+	−	+	−50%	Positive.[2]	43	Chronic, 8 years.
32	F.	−	+	−	−25%	Negative.	112	5 years, Still's disease; child 14 years.
33	F.	+	+	−	−50%	Positive.		Chronic, 14 years.
34	F.	+	+	−	−50%	Positive.	20	3 months' duration.
35	F.	+	+	+	−50%	Positive.	49	Chronic, 5 years; invalid.
36	F.				−50%	Positive.		Chronic.
37	F.				−50%	Positive.		Chronic.
38	F.				−50%	Positive.		Chronic.
39	F.	+			−50%	Positive.		Chronic, severe active disease.
40	F.				−50%	Positive.		Chronic.
41	F.				−50%	Positive.		Chronic, acute exacerbation.
42	F.				−50%	Positive.		Chronic.
43	F.				−50%	Positive.		Chronic.
44	F.				−50%	Positive.		Subacute.
45	F.				−50%	Positive.		Chronic.
46	F.	+			−50%	Positive.		Chronic.
47	F.	+			+	Negative.		Chronic.
48	F.	+			−50%	Positive.		Chronic.
49	F.	+			−50%	Positive.		Chronic.
50	F.	+			−50%	Positive.		Chronic.
51	F.	+			−50%	Positive.		Chronic.

[1] "+", increase; "−", decrease.
[2] "Doubtful" (Case 11), no eosinophile cells present before administration of adrenaline.
[3] Erythrocyte sedimentation rate (Westergren), millimetres in one hour.

This patient was tested before the Dunger technique of counting the eosinophile cells was instituted. Later in most cases the calculation was made from the examination of the blood slide and the Dunger method employed at the same time. In Table II a number of these results are shown. In column A estimation was made from the slides, whilst in column B estimation was made by the Dunger technique.

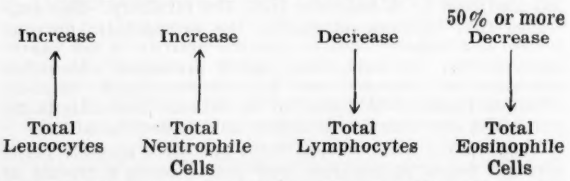
Although the figures differ, the result is the same; that is, both methods reveal a drop of 50% or more of the circulating eosinophile cells during some period of the test.

The Dunger technique is more speedily carried out, and this fact makes it of great importance in public hospitals; but if the lymphocyte and neutrophile cell counts are desired, the slides must be examined.

These tests were carried out in two public hospitals, in clinics and in private practice. The absence of all the data in some instances was due to the fact that the full test, being time-consuming, could not be carried out. It is of paramount importance to know the eosinophile cell count, as this indicates the presence or absence of the quantity of cortisone secreted in response to the stress hormone adrenaline. However, in the 34 cases in which it has been possible to carry out the full test, some interesting facts have been gleaned. The normal response to adrenaline is best illustrated in Case 28, one of early rheumatoid arthritis in a female patient, aged twenty-five years; it consists of an increase in the total leucocyte count and in neutrophile cells, a decrease in lymphocytes after an increase, and a greater than 50% decrease in the number of eosinophile cells also after an increase. In this case the eosinophile cell count to begin with was slightly raised.

The lymphocytosis as seen in this case is a much more common accompaniment of rheumatoid arthritis than is generally recognized, and previously this has generally been regarded as due to chronic sepsis in many cases.

The typical response to adrenaline in a normal person can be diagrammatically shown as follows:



A 50% decrease in the number of eosinophile cells during four hours after the injection of adrenaline constitutes a positive result and indicates a normally reacting hypothalamic, anterior-pituitary adrenal-cortex system; it is positive evidence of the production of cortisone on the one hand, which leads to lymphopenia and eosinopenia, and of ACTH on the other, the latter hormone producing the former steroid. Involution of the thymus and dissolution of the thymocytes also occurs in response to cortisone.

TABLE II.
Eosinophile Cells per Cubic Millimetre.

Time.	Case 6.		Case 7.		Case 8.		Case 9.	
	A.	B.	A.	B.	A.	B.	A.	B.
Before injection of adrenaline	240	340	200	350	80	100	68	200
After injection of adrenaline:								
1 hour	90	200	140	200	130	—	290	600
2 hours	180	100	146	100	152	—	200	120
3 hours	84	100	120	50	—	—	—	—
4 hours	76	50	—	50	166	160	80	100

In Case 22 we also observe the typical normal reaction to adrenaline and the presence of lymphocytosis in the initial leucocyte count (Table IV).

However, variations of response may be observed as in Case 8, in which a positive result was obtained as regards eosinophile cell reduction, while the reactions of the lymphocytes were the reverse of normal (Table V).

It will be noted that the total leucocyte count and neutrophile cell count increased whilst the lymphocyte count also increased. However, the eosinophile cell count makes the result positive—that is, 50% or more reduction, but the response is different from the two former cases. This patient has only partially responded to benzyl sulphanilamide ("Proseptasine") and adrenaline therapy, and although the disease is very active it is not of long duration. A suggestion may be made that the difference in response of the lymphocytes and eosinophile cells in some cases indicates that different hormones are responsible for the two reactions.

TABLE III.

Time.	Total Number of Leucocytes.[1]	Total Number of Neutrophile Cells.[1]	Total Number of Lymphocytes.[1]	Total Number of Eosinophile Cells.[1]
Before injection of adrenaline ..	7800	3410	3278	546
After injection of adrenaline:				
1 hour ..	9800	5488	3430	588
2 hours ..	8000	5760	1120	160
3 hours ..	10,000	7800	1900	200
4 hours ..	8200	6068	1804	164

[1] Per cubic millimetre.

TABLE IV.

Time.	Total Number of Leucocytes.[1]	Total Number of Neutrophile Cells.	Total Number of Lymphocytes.[1]	Total Number of Eosinophile Cells. (Calculated from Slide.)[1]	Eosinophile Cells. (Dunger Technique.)[1]
Before injection of adrenaline	7000	3220	3150	70	50
After injection of adrenaline:					
1 hour ..	12,000	7800	3840	120	100
2 hours ..	9600	7392	1728	—	—
3 hours ..	8400	6384	1680	—	—
4 hours ..	7200	5544	1512	—	50

[1] Per cubic millimetre.

Case 4 has been interesting. The patient, a female, has responded to adrenaline therapy commenced in June, 1948, and given for eighteen months, although the disease has been present for nine years. She had been completely incapacitated and incapable of work for nearly two years before adrenaline therapy was begun and had lost over 18 pounds in weight. Her erythrocyte sedimentation rate had been 40 millimetres (Westergren, at sixty minutes), but at the time of the test it was normal. Clinically she had completely recovered, there being no stiffness and pain, although she had some residual deformity. The results of her test reveal a typical response with an increase in the total number of leucocytes and neutrophile cells and an increase in the lymphocytes at the first hour followed by a decrease, and a decrease in the number of eosinophile cells at the first hour, which suggests that two separate hormones may be responsible for these different reactions. The results of her test are shown in Table VI.

TABLE V.

Time.	Total Number of Leucocytes.[1]	Total Number of Neutrophile Cells.[1]	Total Number of Lymphocytes.[1]	Total Number of Eosinophile Cells.[1]
Before injection of adrenaline ..	8000	6160	1440	80
After injection of adrenaline:				
1 hour ..	13,000	7930	4290	130
2 hours ..	15,200	11,344	3152	152
3 hours ..	10,000	7300	2300	—
4 hours ..	8800	6160	1936	166

[1] Per cubic millimetre.

In patients who have manifested only a slight improvement under adrenaline therapy, we have noticed either that the reduction in the number of circulating lymphocytes has been very small or that an actual rise has occurred. Table VII shows the picture in three such cases.

TABLE VI.

Time.	Total Number of Leucocytes.[1]	Total Number of Neutrophile phile Cells.[1]	Total Number of Lymphocytes.[1]	Total Number of Eosinophile Cells.[1]
Before injection of adrenaline ..	6600	4686	1716	130
After injection of adrenaline:				
1 hour ..	12,600	9828	2268	—
2 hours ..	8700	7134	1372	—
3 hours ..	7200	5688	1224	72
4 hours ..	7200	5760	1190	—

[1] Per cubic millimetre.

In all three cases the number of circulating eosinophile cells decreased to under 50%, so that the test result is positive as judged by these cells but negative in Cases 8 and 10 if judged by the failure of adrenaline to produce a reduction in the number of circulating lumphocytes.

In Case 4, previously mentioned, in which the test was carried out at the end of successful adrenaline therapy of over eighteen months' duration, it may be seen that the

lymphocyte reduction was pronounced at the second, third and fourth hour, and therefore contrasts with the lymphocyte status recorded in Cases 8, 9 and 10.

Case 12 is interesting, because clinical response to "Proseptasine" (benzyl sulphanilamide) therapy and adrenaline has been most pronounced. Generalized rheumatoid arthritis of the upper and lower limbs was associated with a raised erythrocyte sedimentation rate of 74 millimetres (Westergren, at sixty minutes), generalized skin pallor, cyanosis of lips and fingers and pitting œdema of the lower limbs. The duration of illness was nine months, and the patient, a male, had lost over 14 pounds in weight. In three months his erythrocyte sedimentation rate fell from 74 to 16 millimetres in one hour, cyanosis and pallor had disappeared, and his anæmia had diminished, the number of red cells having increased from a little over 3,000,000 to 4,000,000. After this therapy the neutrophile cell count increased whilst the number of lymphocytes fell. During therapy he still maintained his job and carried out his work, though with difficulty. He gained 11 pounds in weight in the following five months, during which time adrenaline therapy was maintained in conjunction with the administration of "Proseptasine" and 750 milligrammes of ascorbic acid by mouth *per diem*. The following table, in view of the successful therapeutic response, is salutary as regards deductions (Table VIII).

TABLE VII.

Time.	Total Number of Circulating Lymphocytes per Cubic Millimetre.		
	Case 8.	Case 9.	Case 10.
Before injection of adrenaline ..	1440	884	1056
After injection of adrenaline :			
1 hour ..	4290	3045	1980
2 hours ..	3152	960	3640
3 hours ..	2300	552	1600
4 hours ..	1936	2400	2000

TABLE VIII.

Time.	Total Number of Leucocytes.[1]	Total Number of Neutrophile Cells.[1]	Total Number of Lymphocytes.[1]	Total Number of Eosinophile Cells. (Slide.)[1]
Before injection of adrenaline ..	8800	5710	2540	88
After injection of adrenaline :				
1 hour ..	13,200	8580	2856	204
2 hours ..	8900	7013	1246	89
3 hours ..	7000	5600	910	210
4 hours ..	7200	5832	864	144

[1] Per cubic millimetre.

This table reveals that, although the normal response occurred as regards increase in the total leucocyte count, increase of neutrophile cells and reduction of lymphocytes, the number of eosinophile cells actually increased. This result also suggests that a different hormone operates in response to adrenaline to produce reduction of lymphocytes and reduction of eosinophile cells. The successful outcome of adrenaline and "Proseptasine" therapy in this case is difficult to account for, if the absence of a typical eosinophile response—that is, more than 50% reduction in the circulating eosinophile cells—is taken as indicating the failure of cortisone production by adrenaline. The absence of reduction in the circulating eosinophile cells should have indicated the failure of adrenaline to stimulate the production of cortisone by way of ACTH and should therefore have militated against its employment as a valuable therapeutic tool. However, the beneficial response to therapy indicates that there is still a gap between theory and practice, and that in the absence of a typical eosinophile response adrenaline may still be of therapeutic importance when combined with continued suppressive sulphonamide therapy. As we have observed some remarkable remissions of rheumatoid arthritis following "Proseptasine" therapy alone, suppression of bacterial antigen by this sulphonamide in this case may be entirely responsible for the successful outcome.

Case 13 is one in which severe generalized rheumatoid arthritis in a man, aged sixty years, was associated with extensive nodule formation; many of the nodules had ulcerated. He failed to respond to adrenaline, insulin and "Proseptasine" therapy. He had lost over two stone in weight, his erythrocyte sedimentation rate was 76 millimetres (Westergren, at sixty minutes), and his general state of nutrition was poor. His response to adrenaline was as shown in Table IX.

TABLE IX.

Time.	Total Number of Leucocytes.[1]	Total Number of Neutrophile Cells.[1]	Total Number of Lymphocytes.[1]	Total Number of Eosinophile Cells. (Slide.)[1]	Eosinophile Cells. (Dunger Technique.)[1]
Before injection of adrenaline	6400	4736	1216	206	300
After injection of adrenaline :					
1 hour ..	12,400	8308	3472	372	400
2 hours ..	12,500	9500	2215	750	400
3 hours ..	8000	5840	1680	240	100
4 hours ..	8800	5896	2464	264	300

[1] Per cubic millimetre.

The total lymphocyte count shows a primary rise followed by a fall and a secondary rise at the end of the fourth hour. As judged by the eosinophile cell count (Dunger technique), but not by the slide technique, the test result may be declared as positive; but the increase in lymphocytes has been observed in other cases to presage a negative therapeutic response to adrenaline therapy. Therapeutically, thymic and mediastinal lymph gland irradiation may be more productive of benefit in such a case and may pave the way for successful stimulation of adrenal cortical activity by subsequent adrenaline therapy. Table IX shows a rise in the total number of circulating neutrophile cells, but also a rise in the total number of circulating lumphocytes. Successful therapy follows a reduction in the total number of circulating lymphocytes by adrenaline therapy.

TABLE X.

Time.	Total Number of Leucocytes.[1]	Total Number of Neutrophile Cells.[1]	Total Number of Lymphocytes.[1]	Total Number of Eosinophile Cells. (Slide.)[1]	Eosinophile Cells. (Dunger Technique.)[1]
Before injection of adrenaline	7000	4620	1890	210	300
After injection of adrenaline :					
1 hour ..	8000	4880	2640	160	150
2 hours ..	8800	6776	1408	88	50
3 hours ..	7600	5472	1900	76	50
4 hours ..	6000	4260	1820	60	50

[1] Per cubic millimetre.

Case 20 was that of a female subject, aged fifty-two years, who had low-grade periarticular arthritis of two months' duration and a normal erythrocyte sedimentation rate of five millimetres (Westergren, at sixty minutes). The results of the adrenaline test are interesting, and are as shown in Table X.

In this case the eosinophile cell response is pronounced; a greater than 50% reduction occurs at the end of the second, third and fourth hours, and would indicate that in this patient the hypothalamic pituitary adrenal-cortex system functions quickly and highly efficiently. On the other hand, the lymphocyte count after its initial rise at the end of one hour does not present a similar continuous reduction. Once again it would seem to indicate that a different hormone was responsible for the production of the lymphocyte and eosinophile reactions.

Case 22 was that of a female patient, aged sixty-six years, who suffered from rheumatoid arthritis of the neck, both shoulders and both knees following a severe cold. The duration of her illness was seven months, her erythrocyte sedimentation rate was 15 millimetres (Westergren, at sixty minutes) and she had lost 14 pounds in weight. The age of the patient and the duration of the disease provided some interesting observations. The following table shows the result of the adrenaline test (Table XI).

TABLE XI.

Time.	Total Number of Leucocytes.[1]	Total Number of Neutrophile Cells.[1]	Total Number of Lymphocytes.[1]	Eosinophile Cells. (Dunger Technique.)[1]
Before injection of adrenaline ..	7000	3220	3150	50
After injection of adrenaline :				
1 hour ..	12,000	7800	3840	100
2 hours ..	9600	7392	1728	—
3 hours ..	8400	6384	1680	—
4 hours ..	7200	5544	1512	50

[1] Per cubic millimetre.

The rise in the neutrophile cell count is considerable, and the fall in the number of circulating lymphocytes is also pronounced, whilst the eosinophile cell count shows a typical positive response. In a patient of this age whose disease was active as judged by the weight loss, the suprarenal cortex responded to adrenaline stimulation. The lymphocytosis observed before adrenaline therapy was pronounced, and, as stated previously, is more common than is generally believed. This result indicates that the suprarenal cortex in the early cases of rheumatoid arthritis even in old age is capable of responding to stress, as in normal healthy people.

TABLE XII.

Time.	Total Number of Leucocytes.[1]	Total Number of Neutrophile Cells.[1]	Total Number of Lymphocytes.[1]	Total Number of Eosinophile Cells. (Slide.)[1]
Before injection of adrenaline ..	13,400	7772	4576	402
After injection of adrenaline :				
1 hour ..	17,600	6160	9504	880
2 hours ..	16,200	5832	9720	324
3 hours ..	14,600	6132	7300	438
4 hours ..	15,200	9729	4864	Nil

[1] Per cubic millimetre.

Case 25 was one of Still's disease of about eight months' duration in a young girl, aged sixteen years. There were involvement of lower and upper limbs and a high erythrocyte sedimentation rate of 75 millimetres (Westergren, at sixty minutes). She had no enlarged peripheral lymph glands and no splenic enlargement. She was allergic to penicillin and the sulphonamides and at one stage of her illness developed myocarditis. She left hospital after her erythrocyte sedimentation rate had fallen to normal—namely, eight millimetres in one hour—and a short while later was readmitted to hospital suffering from circulatory failure due to pneumococcal septicæmia and bilateral suprarenal hæmorrhage. She died after an illness of approximately twenty hours. A post-mortem examination revealed an enlarged thymus, 45 grammes in weight, and extravasations of blood in many organs, especially the suprarenals. In view of the fulminating terminal illness, the adrenaline test result is of particular interest (Table XII).

In this case the total number of leucocytes increased, but the neutrophile cells decreased until the fourth hour, whilst there was a 100% increase in the total number of lymphocytes at the first and second hours and the count was still raised at the end of four hours. As judged by the eosinophile cell count, the result is normal, as at the fourth hour there is an absence of eosinophile cells. However, the enlarged thymus, the fulminating nature of the pneumococcal septicæmia and the failure of the child to combat the disease is indicative of hypofunction of the suprarenal gland. The refractoriness of Still's disease to anti-rheumatoid therapy and the high mortality rate as compared with the disease in adults may well be due to hyperactivity of the thymus and lymphatic system. In view of the high lymphocyte count, X-ray irradiation of the thymus and mediastinal lymph glands might have enabled suprarenal cortical activity to increase and the tragic outcome to be avoided. The normally enlarged thymus in children may be a factor militating against beneficial response to anti-rheumatoid therapy in Still's disease, as compared with adults.

In Case 26 two identical tests were carried out at an interval of eleven days on a patient bedridden for eight years suffering from chronic rheumatoid *arthritis mutilans* of many years' duration; one result was negative and the other positive. The reason for the change was not obvious. The results are as follows (Table XIII).

TABLE XIII.

Total Number of Lymphocytes per Cubic Millimetre.		Total Number of Eosinophile Cells per Cubic Millimetre.	
January 5, 1950.	January 16, 1950.	January 5, 1950.	January 16, 1950.
1044	1333	522	129
4312	1850	324	296
1802	2250	424	270
518	1408	144	320
970	1874	194	312

That without apparent reason the test result could completely change in eleven days in such a case of chronic rheumatoid arthritis is extraordinary.

Case 27 is that of a female patient, aged sixty-nine years, who had been bedridden for two years and had suffered from rheumatoid arthritis for a number of years. She showed a form of the disease characterized by extreme cachexia and dehydration, muscle flaccidity, subluxation of small and large joints, and an erythrocyte sedimentation rate of 132 millimetres (Westergren, at sixty minutes). There was no enlargement of lymph glands or spleen. Her response to adrenaline is as shown in Table XIV.

This case was diagnosed as one of severe hypoadrenia and rheumatoid arthritis. A persistently low total white cell count and a mildly raised lymphocyte count were present. It will be noted that the neutrophile cells increased whilst the lymphocyte count decreased slightly, but the eosinophile cell count increased sixfold. The proportion of eosinophile cells actually rose from 2% to 12% at the end of four hours. The patient's general clinical condition improved under suprarenal cortical extract therapy ("Eschatin").

In Case 31 a slight increase occurred in the total number of leucocytes and a decrease in the number of neutrophile cells in the first, third and fourth hours, also an increase in the number of lymphocytes and a 50% decrease in the number of eosinophile cells.

In Case 32 a decrease occurred in the total white cell count, and a decrease in the number of neutrophile cells until the fourth hour, also a decrease in the number of lymphocytes, but only a 25% decrease in the number of

eosinophile cells. In this case, one of Still's disease with a high erythrocyte sedimentation rate (112 millimetres in the first hour) and lymphocytosis, the patient was later given thymic irradiation with excellent response as regards joint disability and the erythrocyte sedimentation rate. This case will be considered more fully in a later paper.

TABLE XIV.

Time.	Total Number of Leucocytes.[1]	Total Number of Neutrophile Cells.[1]	Total Number of Lymphocytes.[1]	Percentage of Lymphocytes.	Total Number of Eosinophile Cells. (Slide.)[1]
Before injection of adrenaline	2600	494	1872	72	52
After injection of adrenaline:					
1 hour ..	2400	576	1512	63	192
2 hours ..	2500	800	1450	58	100
3 hours ..	2300	575	1449	63	207
4 hours ..	2600	754	1430	55	312

[1] Per cubic millimetre.

In Case 33 the patient, a sufferer from chronic rheumatoid arthritis, had had thymic X-ray irradiation without any great relief; but the adrenaline test revealed a most pronounced increase in the number of white cells, greater than in any other case, an increase in the number of neutrophile cells, a pronounced decrease in the number of lymphocytes, at the third and fourth hour, and also the typical reduction in the number of eosinophile cells. This female patient gave the normal reaction to adrenaline, and this may indicate that adrenaline therapy will now be productive of much improvement due to previous thymic and mediastinal irradiation. This patient had been crippled for many years, and it is seen that the normal reaction to stress occurs in spite of chronicity and severity of the disease. The test was carried out a few months after irradiation. The result of the test is as follows (Table XV).

TABLE XV.

Time.	Total Number of Leucocytes.[1]	Total Number of Neutrophile Cells.[1]	Total Number of Lymphocytes.[1]	Total Number of Eosinophile Cells. (Dunger.)[1]
Before injection of adrenaline ..	5200	3172	1664	150
After injection of adrenaline:				
1 hour ..	9200	4876	3680	300
2 hours ..	14,000	10,990	2240	100
3 hours ..	9200	4646	920	50
4 hours ..	7000	5950	840	—

[1] Per cubic millimetre.

Case 34 was an early case of rheumatoid arthritis of three months' duration; the patient was a woman, aged forty-eight years. The erythrocyte sedimentation rate was 20 millimetres in the first hour, but she had lost 24 pounds in weight and was greatly fatigued. Generalized bilateral arthritis of wrists, fingers, ankles and feet and typical rheumatoid arthritis were present. The adrenaline test revealed a normal response, in that the total number of white cells and neutrophile cells had increased, and the number of lymphocytes and eosinophile cells had decreased, the latter showing a drop of over 50%. In this early case the pituitary adrenal system responded normally to adrenaline and therefore was capable of reacting normally to stress.

In Case 35, one of chronic rheumatoid arthritis with complete invalidity for one year, the lymphocyte count increased, but the adrenaline test produced a typical decrease in the eosinophile cell count. She has responded to "Proseptasine" and adrenaline therapy.

In Case 39 the adrenaline test produced a positive result on December 1, 1949, before thymic irradiation, the eosinophile cells being counted by Dunger's method. After two courses of thymic and mediastinal X-ray irradiation the patient was tested again. The eosinophile cell counts per cubic millimetre are as follows (Table XVI).

TABLE XVI.
Eosinophile Cells per Cubic Millimetre.

Time.	Before Injection of Adrenaline.	After Injection of Adrenaline.			
		One Hour.	Two Hours.	Three Hours.	Four Hours.
Before irradiation (December 1, 1949)	75	250	125	25	100
After irradiation (September 21, 1950)	150	100	125	75	50

It will be noted that the first and second hour increase in the eosinophile cell count on the first occasion was wiped out in the second test, and that whereas the count was greater at the fourth hour in the first test, it was only one-third as compared with the pre-adrenaline injection level in the second. This may indicate that suppression of thymic activity and mediastinal lymph gland activity by irradiation allows a greater cortisone response to adrenaline. Clinically the patient's condition has much improved and the mental outlook has been entirely changed by irradiation. Adrenaline had not been employed therapeutically in this case. After thymic irradiation her erythrocyte sedimentation rate decreased from 60 to 34 millimetres in the first hour (Westergren). After the first course of thymic X-ray irradiation, within two weeks of its commencement the patient could dress herself and put her arms over her head, and needed only ten grains of aspirin daily to relieve stiffness. A slight recurrence of the disease necessitated another course of therapy. After this the test of September 21, 1950, was made and revealed an improvement in cortisone production as measured by the eosinophile cell response at the fourth hour. After thymic and mediastinal irradiation, pain, stiffness, septic hue and disability diminished, and the sedimentation rate greatly improved. The contraction deformity of her knees, however, still requires orthopædic therapy for correction, whilst the upper limbs, less severely affected, responded entirely to the therapy without any auxiliary physiotherapy.

Discussion.

One of the interesting results of our research was that many patients suffering from chronic rheumatoid arthritis gave normal responses to adrenaline, an almost universal feature of the early cases.

These results would seem to indicate that in the majority of cases of rheumatoid arthritis, the pituitary suprarenal cortex system responds normally to adrenaline and therefore normally to stress. This would hardly indicate any abnormality in the pituitary gland or adrenal cortex in the majority of cases of rheumatoid arthritis, and this is borne out by the infrequency of this disease in Addison's disease and by the lack of histological abnormality of the suprarenals in rheumatoid disease. However, the fact remains that cortisone and Compound F in large doses will produce a rapid remission of rheumatoid arthritis, and we have found that adrenaline, which stimulates the production of the glucocorticoids of the suprarenal cortex, is productive of outstanding benefit in febrile rheumatoid arthritis and is often of great value in the chronic vasospastic varieties of the disease. In other words, stimulation of the gland favourably influences the disease. The knowledge that frequently lymphocytosis with enlarged lymph glands is commonly observed in rheumatoid arthritis in children and also in adults, and that when it is present difficulty of treatment is increased, caused the trial of X-ray therapy to the thymus gland and mediastinal lymph glands. We postulated that dissolution of thymocytes and

lymphocytes, as well as the reduction in the size of the lymph glands due to cortisone, might reduce the general sensitivity to stress, bacterial or otherwise, a feature of the so-called *status thymico-lymphaticus*. We have observed that the rheumatoid subject is much more sensitive to sulphonamides and gold therapy than other patients, and postulate that this state of hypersensitivity may be the expression of a hyperactive thymus and lymphatic system in children and in many adults. We have found that X-ray therapy to the thymus and mediastinal lymph glands has produced a remission of rheumatoid arthritis accompanied by a considerable reduction in or return to normal of the erythrocyte sedimentation rate.

The fact that adrenaline failed to produce the normal eosinopenia (50% or more reduction in circulating eosinophile cells) in seven of our 51 patients, and therefore failed to produce adequate cortisone secretion, would discount its therapeutic use in such cases. The patients who fail to respond to adrenaline stimulation given for therapeutic reasons three or four times a day should respond to cortisone. This test may therefore be of value in the division of cases as to their suitability for adrenaline stimulation or cortisone therapy. The fact that adrenaline can produce similar peripheral blood changes (namely, lymphocytopenia and eosinopenia) as does cortisone, and that it does produce an increase in the suprarenal cortex, gives its therapeutic employment a sound scientific basis. The immediate reaction of tremor and palpitation to its parenteral administration may militate against its widespread employment in many cases, but the utilization of adrenaline in oil diminishes those reactions very appreciably and many patients may be given 0·75 to 1·0 millilitre twice a day. However, in the acute cases, especially when fever is present, 0·5 millilitre given four times a day is productive of rapid alteration in signs and symptoms of the disease. The depletion of ascorbic acid and cholesterol in the suprarenal cortex following adrenaline therapy, and the fact that the blood ascorbic acid level is low in rheumatoid arthritis, call for adequate ascorbic acid therapy during the therapeutic employment of adrenaline.

In some cases, especially in afebrile rheumatoid arthritis associated with loss of weight and vasoconstriction, insulin and adrenaline may be of greater benefit, whereas in rheumatoid arthritis in older subjects, in whom cardio-vascular changes prohibit the use of adrenaline, insulin alone constitutes the safer hormone. It may be employed in a dosage of five units or more before each meal.

Conclusion.

In conclusion, we find that, as judged by the adrenaline test, the great majority of rheumatoid patients respond to adrenaline as the normal person does—namely, by a reduction of 50% or more in the eosinophile cells of the peripheral blood. However, examination of the neutrophile cell and lymphocyte counts shows some degree of abnormality. In two cases out of 42, approximately 5%, the leucocyte count decreased instead of increasing approximately 5%. The total neutrophile cell count decreased in three cases out of 34 instead of increasing approximately 9%. The total lymphocyte count increased in eight cases out of 34 instead of decreasing by about 24%. Of the eight cases in which the lymphocyte cell count increased instead of decreasing, in seven there took place the typical eosinophile cell decrease of 50% or more which is regarded as evidence of a normal response in the pituitary adrenal cortex system. If cortisone is the steroid involved, the amount secreted which produced adequate eosinophile cell reduction was insufficient to produce lymphocytic reduction. As judged by the lack of adequate decrease in the eosinophile cells, negative results to the test were a little less than seven out of 51. However, even if the pre-adrenaline lymphocytosis figure of 26% of our cases is taken as suggesting suprarenal cortical hypofunction, it is observed that approximately three-quarters of all rheumatoid subjects have a normally reacting pituitary adrenal cortex system. This conclusion does not rule out a hyperfunctioning thymus and lymphatic system in many rheumatoid subjects, most pronounced in Still's disease, which may well produce sensitivity to bacterial proteins or antigens of various forms, requiring a greater than normal production of adrenal steroids to counter their effect. We are of the opinion that bacterial antigen is probably productive of most cases of rheumatoid arthritis, and that in many subjects of the disease a state of sensitivity exists which we postulate may be brought about by an overacting thymus and lymphatic system, especially in children, but also in adults. In these cases X-ray therapy to the thymus and mediastinal lymph glands is productive of great benefit by reducing the state of sensitivity, which may also be diminished or abolished during cortisone administration.

However, the universal benefit of cortisone in rheumatoid arthritis, on the one hand, considered against the small percentage of cases of lymphocytosis in the same disease, militates against the concept that there is imbalance between the suprarenal cortex and the thymico-lymphatic system in every case of rheumatoid arthritis.

Summary.

1. A review of some of the literature is given regarding the effect of adrenaline on the blood picture.

2. Because of the variability in therapeutic response to adrenaline in rheumatoid arthritis, the adrenaline test was employed to find out the proportion of patients with rheumatoid arthritis who responded or failed to respond in the normal fashion. It was thought that in the acute cases the lesion might be responsive, but that in the chronic cases partial or complete failure might be revealed. A normal response consists of neutrophile leucocytosis, lymphocytosis followed by a decrease below the pre-adrenaline level, and a similar eosinophile cell increase followed by a decrease of 50% or more in the peripheral blood.

3. A table of the response of the total number of leucocytes, the neutrophile cells, lymphocytes and eosinophile cells is given in 34 cases whilst the eosinophile cell response is detailed in 51 cases.

4. Seven out of the 51 patients showed an absence of the typical eosinopenia regarded as an expression of inadequate cortisone secretion in response to adrenaline.

5. A number of typical, atypical and negative responses are given in the various tables and some details of the cases are discussed.

6. Pre-adrenaline lymphocytosis existed in 13 of those patients for whom a full differential leucocyte count was performed. The presence of enlarged lymph glands in Still's disease and frequently in adult rheumatoid arthritis, as well as this lymphocytosis, suggests a possible mild degree of so-called *status thymico-lymphaticus*.

7. The small proportion of failures in the test (seven out of 51) would seem to indicate a normally reacting hypothalamic pituitary adrenal cortex system in the great majority of cases of rheumatoid arthritis.

8. The therapeutic implications of the test are discussed, and methods of employing adrenaline and insulin as well as the variety of cases are briefly considered.

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Reports of Cases.

THE BIRTH OF QUADRUPLETS: A SUCCESSFUL CASE OF PREGNANCY AND CONFINEMENT COMPLICATED BY MULTIPLE PREGNANCY (QUADRUPLETS), PREECLAMPTIC TOXÆMIA AND UTERINE INERTIA.

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AND A. J. OSTINGA,
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With a Note on the Placentæ by B. T. MAYES,
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Clinical Record.

B.S., aged twenty-nine years, was born in England. She had had one previous confinement four years earlier, which was normal after medical induction of labour. No previous serious illnesses were recorded. Her first consultation was on January 6, 1950. Her last menstrual period was in November, 1949, the expected date of her confinement being August 20 to 26. The patient's weight was eight stone ten pounds and her blood pressure was 130 millimetres of mercury, systolic, and 78 millimetres, diastolic. The urine had a specific gravity of 1012 and was clear; all specimens examined were early morning specimens. During January the patient had fairly severe hyperemesis. She was examined at weekly intervals. The hyperemesis cleared up by the end of January, and the patient was examined at monthly intervals until May 30. Her blood pressure remained constant and her urine remained clear. In April the increased size of the uterus suggested the possibility of (i) hydramnios or (ii) twins. The fundus tended to project forward rather than upwards. On May 30 her weight was 10 stone 12 pounds, her blood pressure was 130 millimetres of mercury (systolic) and 78 millimetres (diastolic), and the urine was clear.

Multiplicity was now obvious. It was decided to wait until about thirty-two weeks' gestation for X-ray examination, so that the period of probable development might be ascertained. On June 16 X-ray examination in the antero-posterior position revealed multiplicity; three fœtuses were visible in this X-ray film. On June 27, however, antero-posterior and lateral X-ray films confirmed the presence of quadruplets.

On July 16 her weight was 11 stone, her blood pressure was 145 millimetres of mercury (systolic) and 80 millimetres (diastolic) and the urine was clear. There was some swelling of the feet and ankles. The patient was put to bed for a week and restricted salt in the diet was allowed. From this period onward the question of allowing the fœtuses to become mature whilst controlling toxæmia became the problem. The patient's weight was not recorded from this period onwards.

On July 23 her blood pressure was 140 millimetres of mercury (systolic) and 80 millimetres (diastolic). All œdema had disappeared. The urine was clear, and the patient felt well and wanted to do her housework.

TABLE I.

Date.	Urinary Output. (Fluid Ounces.)	Urinary Albumin.	Blood Pressure. (Systolic/Diastolic. Millimetres of Mercury.)
29.7.50	53	Cloud.	150/90
30.7.50	58	1/3	150/95
1.8.50	40	1/10	150/95
2.8.50	48	2/24	150/95
3.8.50	40	1/20	150/95
4.8.50	42	1/16	150/98
5.8.50	49	1/16	150/98
6.8.50	48	1/8	150/98
7.8.50	46	Cloud	150/98
8.8.50	52	Heavy cloud	150/98
9.8.50	50	1/10	150/96
10.8.50	56	Heavy cloud	150/90
11.8.50	49	Cloud	150/90
12.8.50	54	Cloud	150/90
13.8.50	56	Cloud	148/90
14.8.50	59	Cloud	148/90
15.8.50	53	Heavy cloud	145/90
16.8.50	81[1]	Cloud	145/90

[1] This sudden increase may have been due to rupture of the membranes and liquor included in the measured specimens.

On July 28 her blood pressure was 150 millimetres of mercury (systolic) and 90 millimetres (diastolic). She had slight headache and slight œdema of the feet and ankles, but no œdema in the sacral area or the abdominal wall. A heavy cloud of albumin appeared in the urine for the first time. The patient was admitted to hospital. Ophthalmoscopic examination revealed no apparent changes in the retina.

From this time until the patient was confined a daily estimation of urinary output, a urine examination and estimation of the blood pressure were made. The figures are given in Table I.

During the period from July 29 until labour commenced the patient looked and felt well, she was free of headache, and her only worry was the discomfort caused by the increased weight of the uterus and its contents.

After her admission to hospital, the patient was given a diet consisting of 110 to 120 grammes of protein per day with eggs and fish when available. She was also given vitamin *K*, vitamin *B*, and stilbœstrol (20 milligrammes daily).

On August 16 the patient had frequency of micturition during the evening. At the commencement of the confinement her urine contained a cloud of albumin and her blood pressure was 145 millimetres of mercury (systolic) and 90 millimetres (diastolic). There was no œdema of extremities or of dependent parts. At 11.45 p.m. slight uterine contractions began. Spontaneous rupture of the membranes probably precipitated labour, but the time was uncertain and no forewaters were present at the first vaginal examination.

On August 17 at 1.15 a.m. a mixture containing 15 grains of potassium bromide and five grains of chloral hydrate was given. At 3.30 a.m. there were moderate, painful uterine contractions, somewhat irregular, and an impression was gained of some degree of primary uterine inertia. At 7 a.m. the patient administered "Trilene" to herself because of more severe pains. At 9 a.m. her bowels opened spontaneously and contractions were frequent. At 10 a.m. vaginal examination (all pelvic examinations were vaginal) showed the cervix to be half dilated, thick and soft. The presenting part was a vertex floating, with widely separated sutures. The position was right occipito-posterior with incomplete flexion. At 10.15 a.m. A.P.C. mixture (Australian Pharmaceutical Formulary), 0·5 fluid ounce, with 20 grains of potassium bromide, was given.

At 12.30 p.m. a vaginal examination was made to determine progress; there was slight descent. From now till almost the end of the confinement a severe degree of uterine inertia was present. The general plan adopted was employment of alternate periods of sedation and stimulation. Inertia was a constant source of worry, the uterus "giving up" as soon as resistance to its efforts was encountered. At 2.20 p.m. a further dose of A.P.C. mixture with potassium bromide was given. At 2.45 p.m. a soap and water enema produced a liquid result. The patient became drowsy and generally relaxed, with no contractions.

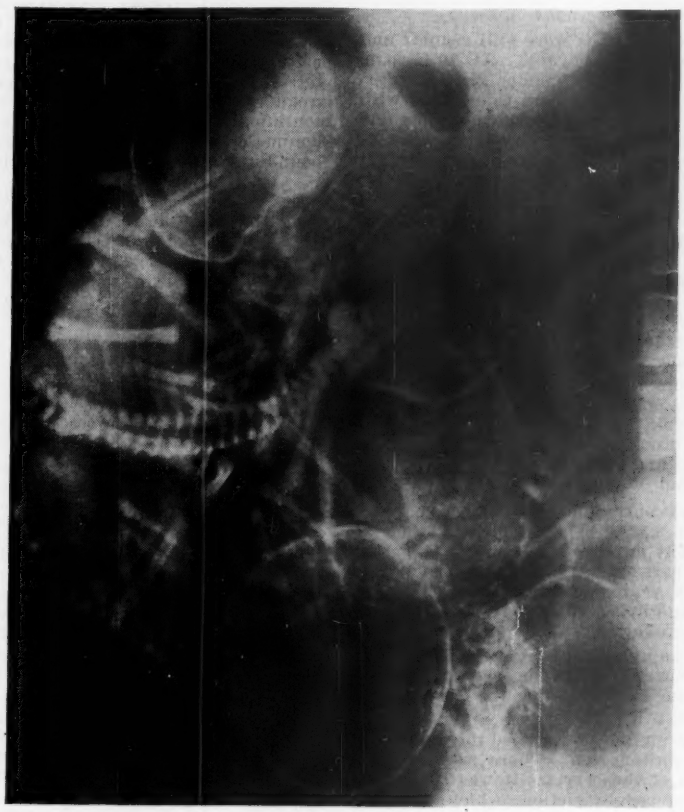

FIGURE I.

At 4 p.m. the maternal pulse rate was 120 per minute, the pulse was full and regular. Oxygen was given intermittently by the nasal route. When the patient was in the lateral position the presenting part became much more mobile. In an attempt to maintain fixation the patient was placed on her back, but discomfort and backache were increased. An intramuscular injection of an aqueous solution of penicillin (125,000 units) was given at this stage for general cover. At 4.45 p.m. slight irregular uterine contractions began.

At 6.30 p.m. a vaginal examination revealed heavy meconium. The head was fixed with slight moulding, but not through the cervix. The cervix was fully dilated, but thick and not retracted; fœtal heart sounds were regular.

At 7 p.m. another dose of A.P.C. mixture with potassium bromide was given.

At 9 p.m. a vaginal examination was made with the patient under general anæsthesia. The occiput had made the short rotation posteriorly. It was decided to rotate the head and draw it down sufficiently to complete the first stage. Thick meconium appeared at this manœuvre. In the interest of the baby forceps traction was applied and delivery was gently attempted. This was successful at 9.16 p.m. The child was a female, and cried spontaneously; her condition improved with oxygen. Rhythmic respiration occurred quickly and the baby was transferred to the nursery. The maternal blood loss amounted to less than one fluid ounce.

At 11.30 p.m. (two and a quarter hours after the delivery of the first baby) there were no contractions, but the uterus had an improved tone. The patient felt more comfortable and had a sensation of lessened abdominal tension. With the expectation of fairly quick deliveries following the first, and in view of the possibility of complications in the third stage, a pudendal nerve block was carried out with 0·5% "Novocain" solution. These expectations were not fulfilled. Vaginal examination revealed a more or less vertex presentation; the head was floating, with some tendency to obliquity towards the right iliac fossa. It was decided to rupture the membranes. A knitting needle was used in an endeavour to prevent cord prolapse. Almost immediately the left fœtal hand covered the fœtal brow, but the vertex was the most dependent part. External manipulation did not improve the position, and it appeared that uterine contractions could advance the head and leave the hand behind. Secondary inertia being established, it was decided to await uterine contractions, and a further period of stimulation was commenced because of the good quality of the fœtal heart sounds.

At 11.38 p.m. an intramuscular injection of three minims of pitocin was given, and this injection was repeated half-hourly for six doses with slight effect. The fœtal heart sounds remained excellent and the maternal condition good. The mother was quite relaxed and very cooperative.

Next day, at 6.30 a.m., the intravenous injection of 500 millilitres of 20% dextrose solution in water was begun; this was completed at 7.10 a.m. Again periods of stimulation were commenced at 8.40 a.m. and at 9.10 a.m. At 10.30 a.m. a vaginal examination showed the position to be *in statu quo*. We were fortified by the good condition of the mother and the fœtus and decided against interference. Intramuscular injections of three minims of pitocin were given at 10.33 and 11.35 a.m. At 12.25 p.m.

the intravenous injection of a further 500 millilitres of 20% dextrose solution in water was commenced; the solution was run in very slowly. At 2.48 p.m. liquor and meconium were draining *per vaginam*; the fœtal heart sounds were good. At 4 p.m. an intramuscular injection of penicillin solution (aqueous—100,000 units) was given, and this was repeated every four hours from now on and during the puerperium.

Interlude.

Between the births of the first and second babies the proceedings were interrupted by the admission to hospital at 9.15 p.m. of another patient pregnant for the second time with a shoulder presentation and a prolapsed arm. By internal version she was delivered of a ten pound nine ounce living baby; the mother promptly went to sleep and we went back to work.

The Remaining Births.

At 10 p.m. the fœtal heart sounds were still regular and good. The position was *in statu quo*. At 10.45 p.m. vaginal examination with the patient under general anæsthesia showed the cervix to be thick and œdematous with no retraction. The head was still riding on the pubis and the hand was now dependent. It was decided to attempt delivery; this was effected by (i) replacement of the arm; (ii) manual traction of the head into the correct axis; (iii) high forceps extraction to the mid-pelvis. The blades were now in the oblique position; they were removed and reapplied, and extraction was completed at 11.8 p.m. The baby was a male, livid and in a state of apnœa; cord pulsations were slow, irregular and intermittent. General resuscitative efforts *plus* the use of lobeline were unsuccessful, and the final response was obtained by mouth-to-mouth insufflation. Maternal hæmorrhage was negligible, and the mothers' general condition was good.

On August 19 at 12.50 a.m. the intravenous administration of 500 millilitres of 20% dextrose solution in water was begun, and the patient was given a further dose of A.P.C. mixture with potassium bromide. She rested well, and her blood pressure, estimated at 8.30 a.m., was 130 millimetres of mercury (systolic) and 70 millimetres (diastolic).

At 9.30 a.m. the uterine contractions recommenced. Weak contractions occurred at 9.33, 9.40 and 9.50, and then at intervals of seven to eight minutes. Abdominal palpation showed the presenting part to be the vertex, which was floating. At 10.30 a.m. a vaginal examination was made; the cervix was thinner and appeared as if it would retract. A period of stimulation followed without effect.

At 2.30 p.m. contractions were regular but unsatisfactory. At 3.40 p.m. surgical rupture of the membranes was effected, no passage of meconium followed and the fœtal heart sounds were satisfactory.

At 5.15 p.m. a vaginal examination revealed the presenting part to be a vertex in full flexion. There was a strong tendency to reformation of the cervix. It was decided to deliver the fœtus by forceps extraction, which was successful at 5.44 p.m. This was a face-to-pubis delivery. The child was a female. The baby made spontaneous respiratory efforts, and this was the strongest quadruplet at birth. The maternal blood loss was negligible. Preparation for the third stage and possible complications began at 6 p.m.; the intravenous injection of 5% dextrose in water was begun slowly, the solution later to be changed to blood or serum as required. Intravenous therapy was to be maintained till the third stage was completed and the uterus firmly and constantly contracted.

At 7.30 p.m. the contractions were regular and moderate; the fœtal heart sounds were good. The fœtus was presenting by the vertex, probably in the anterior position. At 7.50 p.m. contractions were fair only; the patient passed 12 fluid ounces of urine at 10.15 p.m.

At 10.55 p.m. an intramuscular injection of three minims of pitocin was given; the fœtal heart sounds were good, the rate being 140 per minute. At 11.15 p.m. serum was substituted for 5% dextrose solution. At 11.30 p.m. it was decided to rupture the membranes. Immediately after this and after about 200 millilitres of serum had been given, the patient complained bitterly of violent and constant pain, low, dorsal, thoracic and bilateral. She then had her best and most prolonged contraction. This contraction was a very good indication that the third stage might yet be uncomplicated. Under general anæsthesia and through a thick cervix without retraction, forceps extraction was successful. A male child in the left occipito-anterior position was extracted at 11.49 p.m. This baby was livid and in a state of apnœa. Cord pulsations were slow and irregular. General resuscitative measures were started; mouth-to-mouth insufflation was the most successful method. The mother's pulse rate was 140 per minute; the pulse was "bounding". Her blood loss was negligible.

TABLE II.

Date.	Amount of Urine. (Fluid Ounces.)	Albumin Content. (Heaviest Deposit During Twenty-Four Hours.)
17.8.50	32	One-third.
18.8.50	35	One-half.
19.8.50	96	One-eighth.
20.8.50	80	One-half.

The Third Stage.

On August 20 at 12 midnight the giving of small doses (three to five minims) of oxytocic drugs at frequent intervals was the general plan; three doses were given before the delivery of a placenta.

TABLE III.

Baby.	Weight.	Period of Gestation. (Days.)[1]
Alison	3 pounds 9·5 ounces	263
Philip	5 pounds 11 ounces	264
Judith	5 pounds	265
Mark	3 pounds 11 ounces	265

[1] The period of gestation was calculated from the probable evaluation time November 27, 1949, following the last menstrual period on November 13, 1949.

At 12.25 a.m. the patient's bladder was catheterized (12 fluid ounces of urine), so that the necessary manœuvres of the third stage would not be hindered by the bladder. At 12.35 a.m. the placenta was expressed, but not completely. The first to separate consisted of three apparently fused placentæ, the membranes being complete. Still *in utero* was that belonging to the fourth baby. At 12.45 a.m. an intramuscular injection of pitocin was given and the remainder of the placenta was expressed with membranes complete. At 12.50 a.m. the intravenous injection of 500 millilitres of serum was completed and bank blood was substituted. At 1.20 a.m. an intramuscular injection of five minims of pitocin was given. At 1.35 a.m. an intramuscular injection of 0·5 millilitre of ergometrine was administered. At 3.50 a.m. intravenous therapy was stopped; 800 millilitres of blood had been given.

General Observations.

The patient's perineum was intact. The total weight of the placentæ was three pounds seven ounces. The primary blood loss was 25 fluid ounces. Subsequent loss (actual and estimated on linen, clots expressed and retroplacental clots) totalled five ounces.

Anæsthesia.

Anæsthesia during the confinement was as follows: (i) self-administered "Trilene" during the first stage, 7 to 10 a.m. on August 17; (ii) pudendal block as described between the first and second babies; (iii) general anæsthesia with nitrous oxide and oxygen (equal parts) and ether administered for intrauterine manipulations and the applications of forceps. Ether anæsthesia was stopped as soon as the forceps were applied and before traction. The total amount of ether used was four fluid ounces.

TABLE IV.

Day.	Temperature 6 p.m., Pulse and Respiration Rates per Minute.	Position of Fundus.	Urine.	Condition of Bowels.	Lochia.	Diet.	Therapy.	Other Observations.
1	100·8° F.; 24; 100.	Above umbilicus.	70 fluid ounces; albumin content one-half to a cloud.	Bowels open naturally.	Red and moderate in amount.	Protein, 100 grammes.	Penicillin and sulphadiazine administered.	Blood pressure (millimetres of mercury), 148 systolic, 95 diastolic.
2	100° F.; 20; 108.	To umbilicus.	90 fluid ounces; cloud of albumin.	Normal.	Red, slight.	Protein, 100 grammes.	Penicillin and sulphadiazine administered.	
3	Normal all day.	Just below umbilicus.	110 fluid ounces; cloud of albumin.	Normal.	Slight, serous.	Protein, 100 grammes.	Penicillin and sulphadiazine administered.	Lactation commenced; patient sat out of bed.
4	Normal all day.	Four inches above *symphysis pubis.*	110 fluid ounces; cloud of albumin.	Normal.	Slight, serous.	Protein, 100 grammes.	Penicillin and sulphadiazine given.	Lactation satisfactory; patient out of bed.
5	Normal.		130 fluid ounces; cloud of albumin.	Aperient required.	Slight, serous.	Full.	Previous therapy discontinued.	
6	Normal.	3·5 inches above *symphysis pubis.*	106 fluid ounces; urine clear.	Normal.	Slight, serous.	Full.		Blood pressure (millimetres of mercury), 138 systolic, 76 diastolic. Patient walking about.
7	Normal.	Same as previous day.	128 fluid ounces; urine clear.	Normal.	Increased while patient was up.	Full.	Quinine, ergot and strychnine tablets given.	Lactation fairly good; patient walking a little.
8	Normal.	Three inches above *symphysis pubis.*	110 fluid ounces; urine clear.		Slight, serous.			Lactation fairly good; stimulated with a pump.
9	Normal.	2·5 inches above *symphysis pubis.*	88 fluid ounces; urine clear.	Normal.	Slight.			Lactation fair. Blood pressure (millimetres of mercury), 138 systolic, 78 diastolic.
10	Normal.	1·5 inches above *symphysis pubis.*	90 fluid ounces; urine clear.		Slight, serous.			Lactation fairly good. Blood pressure (millimetres of mercury), 136 systolic, 84 diastolic.

The Toxæmia During Confinement.

The toxæmia during the confinement may be summarized as follows. (i) At the onset of labour the patient's blood pressure was 140 millimetres of mercury (systolic) and 90 millimetres (diastolic). The urine contained a cloud of albumin. (ii) During progress up to the birth of the first baby the albumin content of the urine increased to one-third. Between the first and second babies the amount of albumin increased to three-quarters. (iv) Between the second and third babies the amount of albumin diminished to one-eighth. (v) Between the third and fourth babies the albumin content was constant at one-eighth. Examination of the catheter specimen of urine at the beginning of the third stage showed the albumin content to be one-quarter; this twelve hours later increased to one-half, then gradually decreased to a cloud at thirty-six hours.

Urinary Output During Confinement.

The urinary output during confinement is shown in Table II.

Blood Pressure.

The patient's blood pressure twenty-four hours after confinement was 130 millimetres of mercury (systolic) and 70 millimetres (diastolic).

Babies.

Some details concerning the babies are given in Table III.

The babies in general were treated as premature babies for a few hours and then as indicated by their individual needs.

The Puerperium.

Details of the puerperium are given in Table IV.

The Placentæ.

(B.T.M.)

The placentæ consisted of two masses. (i) The larger mass was composed of two placentæ, one of which represented one pair of homozygous fœtuses (probably serving the two females), the other probably serving one of the males. (ii) The smaller mass was one separate and distinct placenta; it was recorded as having come away last, and was connected with the fourth quadruplet to be delivered (a male).

It is therefore suggested that the quadruplets arose from three separate ova, which could have come from either one or both ovaries. Theoretically it is possible that the three ova could arise from one Graafian follicle, as microscopic examination of a Graafian follicle has on more than one occasion shown a follicle to contain three or four ova.

Acknowledgement.

We are indebted to Dr. D. G. Maitland and Dr. J. E. Aiken, of the Department of Radiology, Sydney Hospital, for the skiagram.

Addendum.

On January 25, 1951, the weights of the quadruplets were as follows: Philip, 16 pounds five ounces; Alison, 11 pounds 15 ounces; Judith, 12 pounds one and a quarter ounces; Mark, 13 pounds three ounces.

MASSIVE HÆMOPTYSIS FROM INTRABRONCHIAL FOREIGN BODY.

By HARRY M. WINDSOR,
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THE patient, G.S., a boy, aged eleven years, was first examined on September 1, 1950. He complained that in March, 1950, he had had a sudden hæmoptysis. It soon ceased and he was well until June, 1950, when he had a second hæmoptysis. After this he developed a slight cough and an X-ray examination of his chest in August, 1950, revealed an opaque area in the region of the right cardiophrenic angle. Subsequent questioning elicited interesting details of a pneumonic illness in September, 1949. This illness had followed almost immediately upon an incident at school, in which some boys "got him down" and put a "fox tail" into his mouth.

The patient was admitted to Saint Vincent's Hospital and examined bronchoscopically on September 2. No "fox tail" was found, but repeated delving into the anterior basic bronchus finally produced two microscopic black specks which Dr. John Garvan was able to identify as vegetable material.

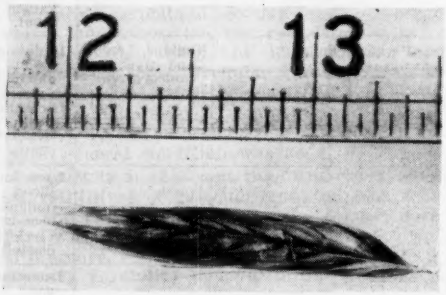

FIGURE I.
Showing specimen of "fox tail" (*Hordeum leporinum*) or barley grass.

After the bronchoscopic examination the boy was ill for a week with right basal pneumonia. It was decided to wait for a month after the pneumonia before proceeding with lobectomy, and in the meantime to carry out a bronchographic examination.

On September 26 a right bronchogram was prepared. Well-developed bronchiectasis of the anterior basic segment was demonstrated. Lobectomy was set down for October 12.

On October 4 the boy had a sudden hæmoptysis (half a pint), and up came the "fox tail". The reaction to this was that perhaps all would now subside, and hopes of avoiding lobectomy were entertained. The subsequent course was as follows. Hæmoptysis occurred on the following dates and in the following amounts: October 5, five ounces; October 6, two ounces; October 7, five ounces; October 8, three ounces; October 9, one pint and five ounces. At this stage the boy's condition gave cause for worry; but conservative measures in the form of heavy chemotherapy were decided upon. In the meantime blood replacement was undertaken.

On October 10, at 10 a.m., just when he had more or less settled down after his hæmorrhage of the previous day, he had another hæmoptysis of 10 ounces. It was decided to carry out lobectomy late in the afternoon, but at midday a further hæmoptysis of one pint and 15 ounces transported the child into a state of exsanguination, asphyxia and terror. Immediate lobectomy was performed.

It was appreciated that asphyxia rather than blood loss was the chief problem. With this danger in mind, after an endeavour to clear the bronchi of blood by bronchoscopic suction, an attempt was made by the surgeon to block the right bronchus with a small McGill blocker. This nearly succeeded in killing the patient, who entered a state of pulseless *asphyxia pallida*. The blocker was hastily removed and a McGill cuffed tube inserted through the glottis. Oxygenation through this cuffed tube produced dramatic improvement, and Dr. Stuart Marshall was able to proceed with what was a perfect anæsthetic.

As asphyxia was still the problem, the patient was placed in a Trendelenburg face-down position and operation was undertaken. As a preliminary step a tape was passed around the right main bronchus and tied tightly over a rubber tube. In this way the right main bronchus was completely occluded and the danger of asphyxia overcome. The engorged, blood-filled lower lobe was quickly removed. During this procedure the middle lobe bronchus was injured, so that a middle lobectomy was required as well.

Convalescence was uneventful. The patient was discharged from hospital on October 28, 1950.

ALCAPTONURIA: REPORT OF AN ADDITIONAL CASE.

By H. G. WILSON,
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ALCAPTONURIA is a condition of disordered metabolism, in which homogentisic acid (dihydroxyphenylacetic acid) is present in the urine. The following case is put on record because the patient is probably the first Australian-born victim of this rare condition.

Clinical Record.

Mr. C.T. was born of Australian-born parents twenty-seven years ago. The parents were not related in any way, and there is no family history of dark urine, arthritis, renal calculi or other abnormality suggesting alcaptonuria. His mother noticed staining of his diapers from his birth. However, he was first examined when applying for life insurance; his urine then reduced Fehling's solution in the cold, which suggested the need for further investigation. At that time he was a member of a friendly society lodge, and had also successfully passed a medical examination for his employment. Questioning revealed that in both instances another urine had been substituted to ensure normal test results.

Further examination of the patient disclosed no other physical abnormality. The urine darkened on standing, reduced Fehling's and Benedict's solutions, and gave the characteristic colour change with dilute ferric chloride solutions. It also gave positive reactions to all the tests mentioned by Basser (1948) and Duncan (1947). Analysis by the method described by Neuberger *et alii* (1947) disclosed varying values, approximately 30.

In June, 1950, the patient's wife was delivered of a female infant, who appeared normal, despite a moderate degree of maternal toxæmia prior to labour. The child's urine did not stain the diapers. It has since been analysed by the method of Neuberger *et alii*, and it contains no discoverable quantity of homogentisic acid.

The condition of any male children to appear in the future will be examined with even greater interest, as alcaptonuria is much more common in males.

Discussion.

The details of this condition have been described adequately by Basser (1948) in his report of the first case to be recorded in Australia. However, it appears that other cases have at times been discovered, though evidently not recorded in the literature.

If Basser's case is the first to be recorded in Australia, then the present patient is the first recorded Australian-born victim of alcaptonuria. Basser's patient was born in Glasgow, but the present patient was born in Australia, of Australian parents.

Further interest is given to the present case by the absence of any family history, and by the fact that the patient has recently become the father of a child who shows no evidence of the condition.

Summary.

1. An additional case of alcaptonuria is reported.
2. The patient appears to be the first Australian-born subject of the condition.
3. There is no obvious hereditary factor in this case.

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PREGNANCY AT TERM COMPLICATED BY ACUTE APPENDICITIS.

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AND

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ACUTE appendicitis in pregnancy is fortunately not a common complication especially at term. In early pregnancy it is agreed that immediate appendicectomy should be performed, but there is considerable divergence of opinion as to the best type of surgical and obstetrical treatment in the last trimester.

The following case illustrates the conservative management of the pregnancy and immediate appendicectomy.

Clinical Record.

Mrs. D.L., aged twenty-five years, was a healthy *primigravida* whose expected date of confinement was July 24, 1950. Her pregnancy had been uneventful until 3 p.m. on July 23, when she developed vague generalized abdominal pains, and four hours later she vomited. Nine hours after the onset of pain it was most severe in the right iliac fossa, where the maximum point of tenderness was just inside the anterior superior iliac spine. There was also some tenderness at the level of the umbilicus, but there was no muscular rigidity. The pregnancy was at term; the fœtus was lying in the left occipito-anterior position and the head was floating above the pelvic brim. The patient had been trained in relaxation exercises and complained that the pain was not relieved by relaxation. Immediate appendicectomy was performed by one of us (A.M.), a low Kocher's incision being used. This allowed excellent access to the mildly inflamed appendix without uterine displacement. The caecum was not as high as usual, having a short mesentery, and this probably accounted for the fact that the pain experienced was not so high as usual.

The convalescence was uneventful. Antibiotics were not administered, but morphine was given every four hours for twenty-four hours.

One week later the patient came into spontaneous labour. The upper abdominal scar did not interfere with the second-stage contractions, and a living female child weighing six pounds 14 ounces was delivered by the low application of forceps. The mother had an uneventful puerperium and breast fed her baby. She was discharged home on the fourteenth day of the puerperium.

Comment.

The progressive upward displacement of the appendix during pregnancy renders the usual McBurney's incision inadequate. The higher incision gave good exposure with minimum handling of the uterus. It was thought that Cæsarean section at the time of operation would have been unwise and hazardous. The outcome of the case certainly justified conservatism, and even in more severe cases the advent of antibiotics may eliminate radical measures. However, it is still important to remember Babler's dictum: "The mortality of appendicitis complicating pregnancy is the mortality of delay."

FIXED DRUG ERUPTIONS: TWO CASES OF IDENTICAL DISTRIBUTION (SULPHADIAZINE).

By ERNEST CHENOWETH, M.D.,

Melbourne.

A FIXED eruption is "a sharply circumscribed eruption which recurs in previously reacting areas after exposure to a medicament or other excitant" (Sulzberger). Such an eruption produced by any other agent than drugs is of the utmost rarity.

In October, 1950, Mrs. C., aged fifty-one years, complained of a symmetrical, irritable, circumscribed rash confined to the upper eyelids. The rash suggested dermatitis of the contact eczematous type, and there had been about nine previous attacks of identical distribution over the past ten years. Exhaustive investigations for a causal contactant were fruitless. Inquiry elicited that one gramme of sulphadiazine had been taken the day before the eruption, and that this drug had also been taken prior to all the other outbreaks.

In January, 1951, Mr. S., aged forty-three years, when undergoing treatment for asthma, mentioned that he had had urticaria of the upper eyelids for the past two days, and that this was the fourth such attack involving this area over the past three years. Examination indicated that the rash was of the allergic dermatitis type, and inquiry elicited that he had taken one gramme of sulphadiazine the night before the attack, and that each previous eruption had been preceded by the taking of sulphadiazine.

In each of the two cases the severity and duration of the rash varied with the duration of administration of the drug on each occasion.

These and similar drug reactions are based on specific acquired sensitivity, and it is interesting to note that drug reactions were included by Pirquet in 1906 among his first examples of allergy. Drug allergies are important because they are amongst the most common—and perhaps also amongst the most commonly overlooked—of all the cutaneous manifestations which confront the medical practitioner. In the case of the fixed variety the number of such lesions can range from one to several hundred, and there is often a sensation of burning or itching; but subjective symptoms may be completely absent. In North America the most common causative agent is phenolphthalein, perhaps because it is about the most widely used of drugs there. In continental Europe phenacetin and antipyrin are the most common. There is a long list of medicaments which can cause fixed eruptions, and it is noteworthy that it bears a close resemblance to the list which may cause blood dyscrasias (granulocytopenia).

Sulzberger states that "the localized sensitivity appears suddenly, without connection with any known local or general disease, or with any pathologic, psychic, nervous or physical state. The sensitivity appears and remains confined to certain areas which do not differ from the adjacent unaffected skin in any known or demonstrable manner".

It is the custom of many patients, with or without their doctor's cognizance, to take various drugs from time to time for minor disabilities both of a local and of a general character, and this should be borne in mind when one is investigating an otherwise baffling eruption.

Reviews.

TEXT-BOOK OF GYNÆCOLOGY.

IT is difficult to produce in one and the same work what is intended as a "textbook for students and as a guide for clinicians". A. H. Curtis and J. W. Huffman have not quite achieved this objective in the sixth edition of their book entitled "A Textbook of Gynecology".

A desirable and valuable feature of the book is that the authors' own views are presented fearlessly, a fact readily understood, considering the long clinical experience upon which these are based. Some of the subjects which they discuss include: the anterior liver surface adhesions as a complication of a pelvic gonorrhœal infection and the importance of recurrent infection as being responsible for most of the permanent damage to pelvic viscera; the use of testosterone in palliative treatment of carcinoma of the cervix; recognition of cervical and uterine obstructions as an important clinical entity responsible for many pathological changes; the superiority of vaginal hysterotomy over curettage for diagnostic purposes; the importance of uterine retroversion in predisposing to other conditions such as endometriosis; that a prolapsed ovary is usually a dysfunctioning ovary; that the affected tube in ectopic gestation is often non-sensitive; an aversion to curettage in the management of incomplete abortion and the rather unusual emphasis on the pathology of the paraurethral ducts and the mesonephric remnants in the cervix.

The book contains unusual concepts and generalizations, some of which, the authors' reputations notwithstanding, may quite justifiably be regarded as still matters of opinion. However, generally it is conservative and sound as well as being up to date. In summary, the presentation of the subject matter appears in many places to be too comprehensive and too complicated for the average uninitiated student, who is usually more receptive of dogma than of theory. On the other hand the book will serve as a "guide" to practitioners.

TOXÆMIA OF PREGNANCY: HUMAN AND VETERINARY.

A VOLUME has been received containing twenty-nine papers presented at a symposium on the toxæmias of pregnancy held at the Ciba Foundation, London, 1950. Here in small compass is the last word in theory and practice on this interesting, disastrous and still unsolved group of conditions. The papers presented for discussion show how different in their essential pathology are some of the most common expressions of gross deviations from the physiological state of pregnancy. The work of the contributors covers a very wide field and it is impossible to enumerate all the subjects discussed; suffice it to say that although a small volume, it contains facts and theories which deal with every aspect of this group of illnesses of men and animals. Of particular interest to Australian readers is the paper entitled "Toxæmias of Pregnancy in the Domestic Animals with Particular Reference to the Sheep" by H. B. Parry, M.R.C.V.S., of the School of Veterinary Science, University of Sydney, and the Animal Health Trust, Newmarket.[2] A group of Dutch workers suggest the conception of an absolute or relative insufficiency of the blood supply to the placenta as a problem for research: in their opinion "toxæmia of pregnancy is caused by any disturbance in the normal relation in the volume of blood carried to the placenta per unit of time and quantity of placental tissue. Toxæmia of pregnancy is a sign of insufficient adjustment of the mother's vascular system to the demands of pregnancy, in other words, it is a disease of insufficient adaption". The relation of nutrition to hepatic disease and toxæmias of pregnancy includes acute yellow atrophy and depends upon three facts: (*a*) endocrine imbalance is of primary importance in the genesis of the clinical picture; (*b*) the liver plays an important role in the maintenance of this balance by virtue of its power of inactivating certain hormones; (*c*) this function of the liver is easily affected by dietary changes. Among other headings of papers are: studies in the circulation in pregnancy both normal and pathological; the calcium level in the diet of the rat during pregnancy and lactation; spastic paralysis and demyelinization in lambs; clinical acetonæmia in cattle; thromboplastin complications; ischæmia of the gravid uterus, placental sex hormones in toxæmias of pregnancy; chorionic gonadotropin; the mono-amine oxidase activity of the placenta; histaminase in normal and pathological pregnancy. The book concludes with summaries from various standpoints; John Hammond deals with the veterinary standpoint, G. W. Pickering the medical and F. J. Browne the obstetric. At the end of each paper the relevant references are set out, there is an index of the whole symposium, and the illustrations vary from simple diagrams of processes to reproductions of photomicrographs of pathological specimens. This volume should be invaluable to general practitioners and obstetricians.

[1] "A Textbook of Gynecology", by A. H. Curtis, M.D., and J. W. Huffman, M.D.; Sixth Edition; 1950. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 9¾" × 6¼", pp. 824, with 466 illustrations, 37 coloured. Price: 95s.

[2] "Toxæmias of Pregnancy: Human and Veterinary: A Ciba Foundation Symposium", edited by John Hammond, M.A., D.Sc., F.R.S., F. J. Browne, M.D., D.Sc., F.R.C.S., F.R.C.O.G., and G. E. W. Wolstenholme, O.B.E., M.B.; 1950. London: J. and A. Churchill, Limited. 8" × 5½", pp. 296, with 93 illustrations. Price: 21s.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Lumbar Puncture and Spinal Analgesia", by R. R. Macintosh, M.A., D.M., F.R.C.S. (Edinburgh), D.A.; 1951. Edinburgh: E. and S. Livingstone, Limited. 8½" × 5½", pp. 157, with 111 illustrations, some in colour. Price: 21s.

Written, among other reasons, to provide a concise exposition of technique to which the newly qualified doctor can refer.

"Handbook of Diagnosis and Treatment of Venereal Diseases", by A. E. W. McLachlan, M.B., Ch.B. (Edinburgh), D.P.H., F.R.S. (Edinburgh); 1951. Edinburgh: E. and S. Livingstone, Limited. 7½" × 5", pp. 376, with 160 illustrations, twenty in colour. Price: 17s. 6d.

Based on instruction given to undergraduate and postgraduate students.

"Preventive Medicine and Public Health: An Introduction for Students and Practitioners", by Fred Grundy, M.D., M.R.C.S., D.P.H.; 1951. Luton: The Leagrave Press, Limited. 8½" × 5½", pp. 300, with 39 figures and some illustrations. Price: 18s.

Gives a bird's-eye view of the scope and practice of preventive medicine.

"Lecture Notes on Emergency Diagnosis Without Laboratory Aid", by Professor Dr. Hanns L. Baur, British Commonwealth Edition, revised by Jean Grant, M.B., M.R.C.P. (Edinburgh). Oxford: Blackwell Scientific Publications. 7½" × 5", pp. 82. Price: 6s.

The object of the book is implicit in the title.

"The Anatomy of Man and Other Animals, or Brothers Under the Skin", by D. Stark Murray, B.Sc., M.B., Ch.B., and Grace M. Jeffree, B.Sc.; 1951. London: Watts and Company. 8¾" × 6", pp. 170, with 57 illustrations, four plates in colour. Price: 18s.

Intended for the scientific and for the "non-scientific" reader.

"Physiotherapy in Obstetrics and Gynæcology (Including Education for Childbirth", by Helen Heardman, M.C.S.P., with forewords by W. C. W. Nixon, M.D., F.R.C.S., F.R.C.O.G., and Veronica Shand, S.R.N., S.C.M., M.T.D.; 1951. Edinburgh: E. and S. Livingstone, Limited. 8½" × 5½", pp. 234, with 94 illustrations. Price: 16s.

Written in response to requests from physiotherapists.

"Micro-Analysis in Medical Biochemistry", by E. J. King, M.A., Ph.D., D.Sc., F.R.I.C.; Second Edition; 1951. London: J. and A. Churchill, Limited. 8½" × 5½", pp. 230, with 22 illustrations. Price: 14s.

Intended for laboratory workers, clinical pathologists and students.

"The 1950 Year Book of Urology (October, 1949-October, 1950)", edited by William Wallace Scott, M.D., Ph.D.; 1951. Chicago: The Year Book Publishers, Incorporated. 8" × 5", pp. 416. Price: $5.00.

One of the Practical Medicine Series of Year Books.

The Medical Journal of Australia

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All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: surname of author, initials of author, year, full title of article, name of journal without abbreviation, volume, number of first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

A MEDICO-SOCIAL PROBLEM IN SOUTH WALES.

THE Medical Research Council of Great Britain has issued a memorandum which must arrest the attention of everyone interested in industrial and social medicine.[1] The authors are P. Hugh-Jones, M.D., M.R.C.P., and C. M. Fletcher, M.D., F.R.C.P., and they write as from the Pneumoconiosis Research Unit of the Medical Research Council at Llandough Hospital, Cardiff. The Medical Research Council states in the preface that up to the present time very little of the information contained in the memorandum has had more than a limited circulation and that it has now been collected together for the first time. It is well that the facts here disclosed should be made known, for much as we pride ouselves on our achievements in industrial and social medicine and in public health generally, we must realize that there remain many unsolved problems and preventible hardships.

From 1931 to 1937 the average annual number of new cases of certified silicosis (certification enabling the affected miner to qualify for compensation) was in Welsh anthracite mines 5·23 per thousand workers; in English and Scottish mines it was only 0·06 per thousand. The non-certifiable condition, so far as its incidence was known, showed a similar disproportion. The publication of reports by the Medical Research Council in 1942 and 1943 on pulmonary disease in south Wales coalminers had two important results. In the first place they provided a stimulus to a campaign of dust suppression in mines; secondly, they led to statutory recognition of "coalworkers' pneumoconiosis" as "fibrosis of the lungs due to silica dust, asbestos dust, or other dust" and including "the condition of the lungs known as dust reticulation". This widened definition increased the number of men eligible for compensation, which, of course, meant compulsory suspension from coalmining. The magnitude of the increase resulted eventually in the setting up of a centre for clinical study and research. The unit established was the "Pneumoconiosis Research Unit", of which Dr. C. M. Fletcher is director and from which the present memorandum comes. From 1931 to the middle of 1948 over 22,000 miners were compelled to leave their work because they had contracted pneumonokoniosis and 85% of them were living in the small mountainous coalfield of south Wales. "In such circumstances there were many who, strongly as they desired new employment, could not hope to find it, even though in recent years most of them have been fit for any but heavy labouring work."

In the memorandum itself Hugh-Jones and Fletcher show that of the 19,000 men certified between 1931 and 1948, some 16,000 survive. These certified men had to seek alternative employment in competition with normal men. They were handicapped in this competition by their disability, by their age (only 20% were under forty years of age), and by their living in the more remote mining valleys, away from the centres of light industry. In the pre-war years very few men found employment; during the war about half of them found work, those failing to do so being mainly the older and more severely disabled. Subsequently large numbers of less disabled men were certified. The upshot is that suitable work is not available and that there are now some 5000 unemployed men with pneumonokoniosis concentrated in the mining valleys of south Wales, of whom three-quarters are probably capable of medium or light industrial employment. Hugh-Jones and Fletcher claim that there is evidence (they made an investigation to determine this) that in jobs not entailing strenuous physical exertion these men give satisfactory service. Their sick rate and absenteeism have been found to be no higher than those of comparable groups of men in three factories investigated. It is unfortunate that some employers have had experience of "a few unrepresentative" men with pneumonokoniosis, who, with a background of compensation, practised wanton absenteeism or used their disease as an excuse for slackness. A certain amount of that kind of behaviour is to be expected, for there are scallywags among men of every trade, profession or calling. It is also true that in the course of time the disability of these men tends to increase and they may have to give up work which for a while they have been able to do. This is stated to be a cause of anxiety to some employers. In a special part of the memorandum some "case histories" are published. It is expressly stated that they are not a representative sample, but merely "a few cases chosen from patients seen at the Pneumoconiosis Research Unit". One man, aged forty-six years, "partially disabled", cannot find a suitable job in a factory. A man, aged forty-five years, certified as in the early stages of pneumonokoniosis, has commuted his compensation claim and has begun to work as a builder—he is a man of enterprise, and apparently an exception. A man, aged thirty-eight years, certified as in the "early stages", finds difficulty in doing heavy work; and another, aged forty-five years, "totally disabled", is doing useful work as a laboratory attendant. A man, aged forty-one years, "partially disabled", has to do night work as a dry cleaner, because he is "not good first thing in the morning". Other cases exemplify the difficulty of finding light work, the difficulty of a long journey to work, and great financial hardship. It is pointed out that men with extreme disablement can be

[1] "The Social Consequences of Pneumoconiosis among Coal Miners in South Wales", by P. Hugh-Jones and C. M. Fletcher; Medical Research Council of the Privy Council Memorandum, Number 25: 1951. London: His Majesty's Stationery Office. 9¼" × 6", pp. 62. Price: 1s. 9d.

employed and some have found work through the Disabled Persons' Employment Corporation. Seriously disabled men often appreciate "something to do" and "it would be an excellent thing if crafts could be organized to employ these ex-miners in their own homes or in village halls". Not unnaturally perhaps, some men are deterred from taking up such work on their own initiative by the fact that they would then be graded as "self-employed persons" and would have to pay full insurance contributions out of their meagre earnings.

One naturally asks what is being or will be done about the distressing facts now "collected for the first time". Previous reports by the Medical Research Council have been effective; it is to be hoped that the present memorandum will not be neglected. It is pointed out that the number of men who will have to leave the mining industry because of disablement by a lung condition will in all probability decrease in the near future. Further, as men die and reach the retiring age, the number will become less and may very well be halved in the next ten years. At the same time it may well be that men in other industries may be recognized as having pneumonokoniosis. Anyhow "the problem will not be static". It is not certain whether the proportion of men who are disabled will change from its present value of 25%, but it "is certain that for several years to come numbers of men now employed will be able to do useful work if only such work can be made available to them". Let us look at the "efforts at improvement" which are being made. *The Disabled Persons (Employment) Act*, 1944, was designed to help people disabled from any cause. Men registered as disabled persons and considered to be in need of "sheltered employment" are eligible in "Remploy" factories or the home work scheme run by the Disabled Persons' Employment Corporation where they have no competition from normal workers. Others may receive an order under the provision which requires employers to take on at least 3% disabled labour. At present 11% of the male working population of south Wales are disabled. We can understand then that the application of the Act in south Wales is difficult. The "Grenfell" factories were intended to cater more specifically for men with pneumonokoniosis, but they have taken long to build and have proved hard to let and "the whole scheme has recently come under considerable criticism". In December, 1949, only 75 men were being employed under the scheme. The Miners' Welfare Commission bought premises intended as a rehabilitation centre for men with pneumonokoniosis, but at present the scheme is in abeyance. The Board of Trade has encouraged private industry to come into south Wales; but while this has reduced unemployment, it has not done so in the special case of men with pneumonokoniosis. From this statement it is clear that all is not being done for south Wales that could be done. As already stated, this memorandum may bring about decisive action. The problem is obviously a medical as well as an industrial one. The work done at Papworth comes to mind, and South Australians, at least, will wonder whether something of the kind that is being done at Adelaide for the tuberculous at Cowan House might not be advocated in part of the southern area of Wales. For such ventures large-hearted persons are needed and we may be sure that Wales has them. The initiation of such movements can have nothing but a beneficial action on the morale of a community. When morale is high adversity seems less, and action not only appears to be worth while, but is the more easily undertaken.

Current Comment.

BATTLE CASUALTIES FROM KOREA.

A RECENT article by Surgeon-Commander R. M. Latta on battle casualties from Korea[1] has aroused interest and comment. This is not surprising, as articles on battle casualties have again become something of a novelty; but more significant than this are the disturbing surgical facts, crying for comment, that it reveals. Latta bases his observations on some 1850 patients carried from Korea to base hospitals in Japan by His Majesty's Hospital Ship *Maine* during the first two months of the Korean war. They included approximately 230 with major soft-tissue wounds without bone involvement, 180 with major compound fractures, and 400 with relatively minor wounds. Smaller groups were 82 with thoracic or thoraco-abdominal wounds, 40 with abdominal injuries, 19 with head injuries and 19 with severe burns. These are not large figures (though any battle casualty is one too many), but they are sufficient to indicate the type and quality of the forward surgery at the beginning of the campaign. It was by no means above reproach. Latta's article is written in no spirit of carping criticism—it is mainly a simple statement of facts—and he explains in a subsequent letter[2] that it was not his intention to criticize the work of other surgeons; he had no first-hand experience of the difficulties they had to overcome, the United Nations forces being at the time penned into a small area around Pusan and the degree of organization being much less than it later became. It is always as well to bear in mind the possible difficulties experienced by the medical services when one comments on the management of battle casualties, and they must be given due allowance in this instance; but some of the faulty practices Latta mentions have no relation to enforced haste or inadequate facilities. Of the 410 patients with major wounds involving soft tissue and/or bone, 51 required further surgical treatment during the short time they were on board, which was mostly about forty-eight hours. In these cases the surgical treatment had been either inadequate (insufficient surgical toilet of the wound) or over-optimistic (ill-advised primary suture). The impression gained is that too much reliance had been placed on antibiotic therapy, which was a routine measure. Latta does not question its value, but asserts that it cannot take the place of surgery in the treatment of war wounds. It has made primary suture feasible under suitable conditions, but suitable conditions cannot be relied upon; under the conditions which war imposes, primary suture is not without risk. Two men had to have their legs amputated probably only because a foot wound had been closed, and "almost every wound which had been closed had to be opened and have further excision done". There were three cases of clinical gas-gangrene; all three patients had had routine penicillin therapy from shortly after the time of wounding, but "primary surgical treatment had not been adequate". Other cases of gas-gangrene are known to have occurred, despite the general use of antibiotics. Hæmorrhage caused little trouble (the patients were mostly handed on again before the usual time for secondary hæmorrhage), but plugs of gauze, plain or impregnated with soft paraffin, had to be removed at the first opportunity; sometimes the dressings over plugged wounds were fixed in place with "encircling turns of adhesive plaster, which naturally soon became tourniquets". Plasters applied to limbs with compounds fractures were not split at first, and this had to be done in almost all cases. Latta urges that plasters should be split in their full length as soon as they are applied and that the division should include

[1] *The Lancet*, January 27, 1951.
[2] *Ibidem*, March 31, 1951.

bandages used to fix dressings under the plaster. He also points out the advantages of writing a routine description of the underlying injuries, perhaps with a sketch, on the outside of the plaster shell.

These are only a few points from an article that contains much interesting material, and it should not be thought that it is just a catalogue of mistakes. The faults have been picked out for comment because it is difficult to believe that they were all unavoidable, in the light of the experience of two world wars. The article has brought a rapid response in *The Lancet's* correspondence columns, headed by a letter from Sir Heneage Ogilvie.[1] Ogilvie's opening paragraph sums up the position:

> Few things in medicine are more regrettable than the repetition of mistakes already made, corrected, and recorded. . . . The problems of war surgery are fundamentally the same in all wars, and though the advent of fresh drugs and fresh methods may modify the details of treatment, the basic details remain the same. The duty of the medical directorate, and of the consulting surgeon in any theatre of war, is to keep those principles before the surgeons who are doing the work, and to insist that they be followed. It should be a simple task; it has proved an impossible one.

Successive campaigns have seen the old lessons unlearnt as surgeons, often skilled in their normal field, refuse to admit that they are tiros in the management of war wounds. So we have the inopportune primary suture, the unsplit plaster cast, the strangulating adhesive bandage, the general failure to appreciate that what is suitable for the patient in hospital will not do for the wounded man on the line of evacuation. There is no need for ignorance. Experienced surgeons of both world wars would presumably be only too willing to pass on their knowledge, and, as Ogilvie asks, "Are there no copies of the 'Field Surgery Pocket Book' available?" It seems that practical activity in these matters is needed. Another correspondent, R. Rutherford,[2] suggests that in every medical teaching centre there should be a chair of military surgery, preferably filled by one who has actually operated in the field. This is scarcely a practical measure, but at least it is a positive suggestion; it is a starting point for the working out of some plan for teaching younger surgeons the lessons they need to know if they are to have the management of battle casualties and, to some degree at least, of the civilian casualties of war. J. A. Shepherd[3] comments: "The non-medical branches of the Services in peace-time prepare for war, but for some reason the doctors do not." This statement may not be absolutely true, but it has sufficient truth in it to set us thinking.

ARTIFICIAL RESPIRATION.

ARTIFICIAL RESPIRATION by manual methods is just the sort of subject to arouse controversy between the theorist and the practical man. Most people know something about it, and many people consider that they know all about it—or at least all that is worth knowing. However, the variety of methods that have been put forward over the years indicates the difficulty experienced in finding the ideal procedure. A valuable contribution to the subject has been recently made in two articles;[4] one, by A. S. Gordon, D. C. Fairer and A. C. Ivy, is published with the authorization of the Council on Physical Medicine and Rehabilitation of the American Medical Association, and the other, by Gordon and Ivy with F. Raymon and M. Sadove, supplements the first report. It is pointed out here that both the theorist and the practical man have their place in the critical evaluation of manual methods of artificial respiration; field tests are necessary, to determine the practicability and adequacy of suggested methods, but "the practical utilization of any manual resuscitation procedure must stem from results obtained under ideal or controlled experimental conditions, because of the numerous uncontrolled factors incident to field testing". The reports are concerned primarily with the experimental aspects. For this work anatomical considerations preclude the use of animals, but three types of human subjects can be used: non-rigid corpses, immediately after death; conscious normal subjects, trained to suspend respiration voluntarily or to hyperventilate to the point of apnœa; normal subjects rendered apnœic by curare (or similar preparation) and/or anæsthetic agents. In the first of the reports results with the first two types of subjects are recorded; results with the third type are in the supplementary article. The numbers of subjects were considerably larger than those usually used for investigation of this subject (109 warm corpses, nine normal subjects with voluntarily suspended respiration after hyperventilation, and 11 normal subjects with respiration passively suspended by means of thiopental sodium, *d*-tubocurarine chloride and a cyclopropane-oxygen mixture); this, with the fact that the effectiveness of various methods of resuscitation was compared on the same subjects, makes the results of unusual interest. The manual methods used, most of which will be familiar to those interested in this subject, were as follows: the Schafer method, which depends essentially on "prone pressure"; the Silvester method, which incorporates "push" and "pull" manœuvres with the patient supine; the Nielsen method, which involves arm lifting ("pull") and scapular pressure ("push"); the Schafer-Nielsen-Drinker method, devised by Drinker, which is essentially the Nielsen method with the Schafer prone pressure substituted for scapular pressure and so involves "push" and "pull"; the Emerson method, in which the hips are raised and lowered with the patient prone, thus producing active inspiration by "pull"; a modification of this, in which only one hip is raised, the patient being "rolled" onto the operator's knee; the Schafer-Emerson-Ivy Method, in which raising of the hips is alternated with pressure on the lower part of the thorax; a modification of this, in which the "rolling" manœuvre is combined with the Schafer method. In addition to these manual methods, the well-known Eve rocking method and certain mechanical methods were used.

The reports contain a great deal of detail that will be of interest and value to those actively concerned with this subject, but it will be sufficient here to refer to the main points in the results obtained. The relative efficiency of the methods was gauged essentially in accordance with the minute volume of pulmonary ventilation. An over-all finding was that the ventilation accomplished on the totally apnœic subjects was approximately twice, and that on the subjects with passive suspension of respiration was three times, that on the warm corpses. All methods involving a "push" and a "pull", thereby causing active inspiration and active expiration, were approximately twice as effective as the "push" or "pull" methods alone. Certain methods are better suited to specific body types, but in the final analysis, the method involving hip lifting and prone pressure was found to be generally most effective—this is Ivy's combination of the Emerson and Schafer methods. The modification of this in which the "rolling" method of lifting one hip is substituted for lifting of both hips is easier for sustained operation and has much to commend it. The Nielsen (arm lift—scapular pressure) method produces comparable amounts of ventilation, but is not free from possible risk of shoulder injury. Mechanical methods are of considerable value, but the important point is made that they are not usually immediately available; since the first few minutes are crucial for resuscitation, mechanical devices must always be considered as adjuncts to, and not substitutes for, manual methods. A manual method or mouth-to-mouth breathing must always be used until an approved mechanical method is available. For the rest we must refer those interested to the original articles; they are full of detailed information of both theoretical and practical value, are well illustrated and will repay careful reading.

[1] *Ibidem*, March 3, 1951.
[2] *Ibidem*, March 10, 1951.
[3] *Ibidem*, March 17, 1951.
[4] *The Journal of the American Medical Association*, December 23, 1950.

Abstracts from Medical Literature.

PÆDIATRICS.

Anoxia and Fœtal Anomalies.

THEODORE H. INGALLS *et alii* (*American Journal of Diseases of Children*, July, 1950), continuing their work on noxious influences during pregnancy, have demonstrated the effect of maternal anoxia on the offspring of the white mouse. Animals at various stages of pregnancy were submitted to rarefied atmospheres. The anoxia resulted in fœtal death or congenital anomalies, the effect on the fœtus varying with the degree of anoxia and the stage of pregnancy at which it occurred. The most severe degree of anoxia caused fœtal death. Two congenital anomalies that were repeated were anencephaly occurring in litters exposed on the eighth day of pregnancy, and cleft palate in those exposed on the thirteenth or fourteenth day. The authors state that these findings add confirmation to the view already strongly held that the tissue most sensitive to damage is that which is in the most active stage of primitive development, and that there is a critical period for many congenital lesions.

Problems in Children of Average or Superior Intelligence.

ANNA-LISA ANNELL (*The Journal of Mental Science*, October, 1949) states that a transient deterioration in school work during adolescence is very common and that the conflicts of puberty are often felt particularly intensely by gifted, intellectually well-differentiated children. She classes the children into several groups. The sub-vital asthenic children become tired only late in the evening and take some time to fall into a deep sleep; they wake heavily and are fully efficient only some hours later; their school efficiency and their appetite are poor in the morning. The ixothymic (sticky) type have slow processes of thinking and some intellectual rigidity, finding difficulty in changing rapidly from one train of thought to another; better achievement has resulted from studying one subject for a day or a week at a time. Children with motor disturbances, due to immaturity, disturbances of internal secretions or the sequelæ of organic diseases, form another group; sometimes these are associated with mental backwardness, for example, in speech; others result from mild hypopituitary dysfunction and the slowness results in difficulties with gymnastics and in writing from dictation. The asthenic type are affected with fatigability, while others have increased muscular tension. The author states that understanding of the physical limitations peculiar to individual children will enable better use to be made of their innate abilities.

Hoarseness in Children.

J. M. LORÉ (*Archives of Otolaryngology*, June, 1950) discusses 56 children, aged fourteen years or less, suffering from speech disorders; 19 had laryngeal abnormalities and 17 had lesions of the true vocal cords, 14 being thickenings and polypoid changes which were bilateral in six. Two had multiple papillomata, bilateral in both cases, one had a small band at the anterior commissure, one œdematous ventricular bands and one loose corniculate and cuneiform cartilages which tended to be drawn into the larynx on inspiration. There was a history of respiratory infection, enlarged tonsils and adenoids or deviation of the nasal septum in a large proportion of the cases. If the thickening of the vocal cord was minimal, conservative treatment was instituted. This included functional rest and the use of medications for treatment of the larynx, nose and sinuses. In only one of the 19 cases could the patient be regarded as cured by this method. Several others showed some improvement. The remainder were advised to undergo some surgical procedure. Only six submitted, two with multiple papillomata and four with polyposis. In the laryngeal operation the stripping technique was employed. Under general anæsthesia and through an anterior commissure laryngoscope, the growth was seized and stripped away *in toto*. Only one cord was treated at a time in order to avoid web formation. When necessary the other cord was stripped one month later. The patients were allowed to use the voice immediately after the operation. Maximum improvement was attained in about one month. After operation the patients were treated by a speech therapist to ensure proper use of the voice.

Wilms's Tumour.

ROBERT E. GRASS and EDWARD B. D. NEUHAUSER (*Pediatrics*, December, 1950) discuss the treatment of embryoma of the kidney. They state that the cells of these very malignant tumours may be undifferentiated, or may form primitive epithelium, muscle, bone or cartilage. They arise presumably from an embryonic rest within the kidney and may grow to a very large size without rupturing the renal capsule and so without invading adjacent structures. Abdominal distension or the finding of a mass in the abdomen is usually the first warning, but hæmaturia occasionally occurs and is of bad omen. Pain is unusual. Pyelography shows the pelvis of the kidney pushed to one side of the mass, distorted and displaced. It may be difficult to distinguish embryoma from neuroblastoma, which has a more "pebbly" surface and a greater tendency to cross the mid-line. If metastasis has occurred, it tends to be to the lungs from an embryoma and to the bones from a neuroblastoma. Cures have been reported by treatment with irradiation alone, nephrectomy alone and a combination of the two. A survey of all cases occurring in the Children's Hospital of Boston since 1914 shows a very great improvement in survival rate. In the period from 1914 to 1930, when treatment was somewhat haphazard, the survival rate was 14·9%. In the period from 1931 to 1939, when William Ladd improved the operative management, paying attention to proper treatment of shock and suitable anæsthesia, and using a transabdominal approach to facilitate removal of large growths and early ligation of renal vessels, the survival rate rose to 32·2%. During the period from 1940 to 1947 the survival rate has been 47·3%. The operative management has been essentially the same. Post-operative irradiation has been the rule; it is commenced as soon as the operation is completed and before the patient recovers from the anæsthesia. Pre-operative irradiation has not been used; it does reduce the size of the tumour and so facilitates operation, but it necessitates delay in operation, causes liquefaction of the tumour mass and may increase the risk of metastasis. Intensive irradiation of any infiltrating tumour left in the abdomen or of small lung metastases seems worth while. The results with infants under the age of one year are much better than with older children, perhaps because infants' abdomens are felt more often by mothers and physicians and so diagnosis may be made earlier.

Sequelæ of Neo-natal Asphyxia.

W. A. B. CAMPBELL, E. A. CHEESEMAN and ANNE W. KILPATRICK (*Archives of Disease in Childhood*, December, 1950) report a follow-up of the children born in the Royal Maternity Hospital, Belfast, during the years 1938 to 1941 with severe *asphyxia neonatorum* (89 children) and of a group of unselected controls (178 children). Subjects included in the asphyxia group were those who as babies suffered from *asphyxia pallida* or *livida* lasting for a stated period of over two minutes. The authors state that after the making of due allowance for relevant concomitant factors, no significant difference has been found in the average physical measurements (height, weight, inspired chest measurement and chest expansion) or in hæmoglobin levels or in intelligence distributions (as assessed from Raven's matrices) between the asphyxia and the control group. This survey gives no support for the hypothesis that *asphyxia neonatorum* is a common cause of later physical or mental retardation.

Survival of Premature Infants.

MORRIS STEINER and WILLIAM POMERANCE (*Pediatrics*, December, 1950) have investigated the survival rate among 791 liveborn premature infants born in the Jewish Hospital of Brooklyn from 1941 to 1945. They found that the survival rate varied directly with fœtal maturity and birth weight, but for any given weight group the outlook for the infant improved in proportion to the degree of its maturity. This was specially striking in infants weighing less than 1500 grammes (approximately three and one-third pounds).

Intracranial Irritation in the Newborn.

W. S. CRAIG (*Archives of Disease in Childhood*, December, 1950) describes varying degrees of intracranial irritation of the newborn in 593 cases. In a large number of these the evidence of intracranial irritation was slight. In 168 cases it was considerable or great, but in the remaining 425 it was slight, consisting of nothing more than such signs as unnatural alertness, disinclination to sleep and "jumpiness" when approached, or fragility with a feeble whining cry and disinclination to suck. The author was able to follow 472 of these children for one year, 361 for three years and 306 for five years. In only 52 of them did he find physical or mental sequelæ of the neo-natal cerebral irritation, and a considerable pro-

portion of the sequelæ arose in children whose original symptoms had not been severe. Physical defect alone occurred in 19 cases, mental defect alone in nine, both physical and mental defect in 20, and convulsions in 18; four children of the last-mentioned group had no other physical or mental damage. The author includes a summary of the ante-natal and natal history and the salient features of the neo-natal illness of each child in whom evidence of permanent brain damage was found.

The Risk of Poliomyelitis after Tonsillectomy.

G. W. ANDERSON, G. ANDERSON, A. E. SHAAR and F. SANDLER (*Annals of Otology, Rhinology and Laryngology*, September, 1950) record a series of 21 cases of poliomyelitis occurring within a month after tonsil removal during the period of an epidemic in Minnesota, United States of America, in 1946. Detailed epidemiological histories were obtained in 2709 cases. In 19 of these the patient had had tonsillectomy or adenoidectomy during the previous month, and in 12 such cases the disease was bulbar (63·2%). During the entire outbreak 20% of all the patients and 11% of those under the age of twelve years had bulbar infection. All except two of the post-tonsillectomy patients were between three and seven years of age—that is, 17 patients. Sixteen of these patients had their operations performed between specified dates. During this same period 508 children of the same age group developed poliomyelitis in the State, 491 of whom had not had a recent tonsillectomy or adenoidectomy. It is estimated that 2686 tonsil and adenoid operations were performed on children of the three to seven years age group between the same dates. Of this group 16 developed poliomyelitis, or a ratio of one to 168 operations (0·60%). It is estimated from statistical data that the number of children of the three to seven years age group in the State, excluding those recently operated upon, was between 220,000 and 260,000. Of those, 491 developed poliomyelitis, making an attack rate of 0·19% to 0·22%. The attack rate for the group whose tonsils were removed during the preceding month was thus three times greater than that among those not undergoing such operations. The bulbar attack rate in the operated group was one to 224 (0·45%), and in the total population of the same age group it was one to 2508 (0·04%), a rate only one-eleventh of that in the tonsillectomized group. While the number of cases is small, it is considered that the difference in the figures is statistically significant.

Glutamic Acid and Mental Function.

HAROLD G. LOEB and READ D. TUDDENHAM (*Pediatrics*, July, 1950) have attempted to assess whether or not glutamic acid has any beneficial effect in improving the mental function of retarded adolescents. The subjects were 33 institution patients, divided into two well-matched groups. In one group each patient was given 24 grammes of monosodium glutamate by mouth each day for seventeen weeks. Patients in the control group were given a placebo in the same way and at the same time. Before and after the experimental period the following psychological tests were carried out: the Stanford-Binet, the Cornell-Coxe ability scale, the Porteus maze, the Thurstone and Thurstone primary mental abilities and the Rorschach. No significant difference between control and experimental subjects could be shown, and it was concluded that glutamic acid produced no benefit in these feeble-minded patients.

ORTHOPÆDICS.

Joint Débridement for Osteoarthritis of the Knee.

BRUNO ISSERLIN (*The Journal of Bone and Joint Surgery*, August, 1950) states that "joint debridement" is a term introduced by Magnuson (1941) to describe an operation on the knee in which all the accessible synovial membrane, osteophytes, diseased cartilage and abnormal soft tissues are removed in an effort to relieve the symptoms of osteoarthritis. He records the results of 35 operations performed on 32 patients during the last eight years; the series includes all those patients whom it was possible to trace and examine twelve months or more after their operation. He states that experience has shown it to be wise to reserve operation for cases of persistent pain with swelling and moderate instability of the knee, in patients who have not obtained relief from conservative measures. The joint should not be too grossly disorganized, for the aim is to relieve pain and yet to preserve useful movement. The patients must be those who are capable of cooperating in the after-treatment, which is quite painful at the time just after operation. The only fixation used after operation is a compression bandage. Quadriceps exercises are begun as soon as possible and active movements after a few days. Weight can usually be taken on the leg after three weeks. The recovery of flexion may be aided by cautious manipulation after five or six weeks, but only if the range at that time is less than 50°. The range of movement may be expected to improve for twelve months. The author states that the operation was considered a success if the patient's pain was abolished or greatly relieved, if the knee retained or regained nearly full extension and movement through a right angle, and if the joint became stable enough for normal activity. These conditions were fulfilled, after 23 of the 35 operations, in 22 patients.

Oxidized Cellulose and Cortisone in the Prevention of Excess Bone and Fibrous-Tissue Formation.

FRANK E. STINCHFIELD (*The Journal of Bone and Joint Surgery*, October, 1950) considered that oxidized cellulose (absorbable gauze) might reduce excess bone formation following joint surgery. In experimental work with dogs it was interposed between fracture fragments, and complete non-union developed. It was used clinically in 22 joint arthroplasties and in 20 cases in which the prime purpose was to limit recurrence of bone production, as in the removal of exostoses, in *myositis ossificans*, and in resection of radial heads. In the arthroplasty series the patients seemed to be comfortable after operation, and the degree of motion was greater than that achieved without the addition of oxidized cellulose. The author discusses how the gauze in the immediate proximity of the bleeding bone interferes with the normal process of bone production. He states that although bone formation could be inhibited by the use of oxidized cellulose, fibrous-tissue formation progressed normally or at an accelerated rate. Therefore, some means was needed of retarding the growth of fibrous tissue in order to overcome another major complication in traumatized joints and in joint arthroplasties. It has been shown that wound healing is inhibited by the administration of cortisone, and it is suggested that the catabolic effect of hyperadrenalism on protein metabolism may account for the decreased activity of mesenchymal tissues. The cortisone hinders degeneration of collagen and thus prevents fibroplastic proliferation. In operations on the right hips of 12 dogs, cortisone was injected into the hip and in some cases was also administered systemically. The result was less thickening of the capsule, more free motion, less crepitation and no inflammatory reaction. The author suggests from this that cortisone has much to recommend it when inhibition of fibrous-tissue formation is desired. Its chief value is in its direct effect locally at the site of surgery, where theoretically it retards the enzyme, or allergic manifestation, producing fibrous and connective-tissue formation. Local injection of cortisone, together with systemic intramuscular administration, appears to offer the greatest help in preventing fibrous-tissue formation. With these facts in mind, clinical application has been initiated. Sufficient time has not elapsed to evaluate the results in humans. However, so far they are encouraging and may contribute toward a lowering of the percentage of complications related to fibrous-tissue and bone formation following operative orthopædic procedures.

Marie Strümpell Arthritis.

LENOX D. BAKER, R. W. COONRAD, ROBERT J. REEVES and W. A. HOYT (*The Journal of Bone and Joint Surgery*, October, 1951) have found that in a series of 100 patients with Marie-Strümpell arthritis, treated by radiotherapy *plus* corrective measures, the results, based on relief of pain, range of motion and radiographic changes, indicate that the therapy can be expected to give approximately the same relief from pain during any stage of the disease. Increase in range of motion can be expected in a fair percentage of the mild and moderately advanced cases. Although there is relief from pain, a decrease in range of motion and further ossification may occur. In the mild or moderately advanced cases, the process can be arrested and in some instances cleared by the radiotherapy. Of the 47 patients in the mild and moderately advanced groups, 15 showed radiographic clearing of the bone changes; 24 showed no change or advance in the disease; only seven showed advance with additional ossification. Comparison with the advanced group of 32 patients shows that radiographic improvement can be expected in the earlier cases more frequently than in the advanced cases, in which the changes are no longer reversible.

Special Article.

THE TERRITORY OF PAPUA AND NEW GUINEA EXPANDS ITS HEALTH PROGRAMME.

STATEMENTS have been made since 1945 by at least two Ministers of State for External Territories that their Governments are determined to bring better health to the peoples of Papua and New Guinea, through an expanded health service.

As recently as December, 1950, the Honourable the Minister for External Territories, Mr. P. C. Spender, K.C., M.P., announced that the Commonwealth Government was to commence with an extensive programme for the construction of hospitals in the Territory of Papua and New Guinea. The Minister for External Territories referred to his earlier announcement that the Government had approved of a programme for the construction of hospitals throughout the Territory at a cost of about £7,000,000. Mr. Spender said that, as part of this programme, he had now approved of the plans for the base hospitals that were to be built at Port Moresby and Lae at a total estimated cost of about £1,750,000. It was intended that the work would be commenced as soon as possible.

Confirming his earlier announcement in the matter, Mr. Spender said that, with a view to preventing this major construction work from adding to the inflationary factors already affecting the Australian economy, it was the Government's intention that the work would be carried out in such a way as to avoid the imposition of any drain on Australian resources of labour and material.

The present expenditure by the Administration is more than ten times greater than any pre-war figure in order to bring about this programme of an expanding health service.

More than 100,000 patients are being admitted as in-patients annually.

Many readers who fought through the New Guinea campaign will be aware of the vast problems that exist to bring better sanitation to the primitive people of this Territory. A delightful article in THE MEDICAL JOURNAL OF AUSTRALIA of September 30, 1944, "Papuan Interlude", by C. H. W. Lawes and B. T. Keon-Cohen, which is well worth re-reading, portrays many of these problems.

The Governments of the Commonwealth of Australia have stressed the necessity to develop the Territory economically —a Territory which is capable of providing Australia with all her requirements of tropical products, which must now be imported from doubtful sources. This vast Territory, with an area of some 180,000 square miles and a population of 1,500,000, is a rugged country from the wet tropic climate of the coastal plains, with their swamps and many river systems, through the rain forests to the cool and fertile central highlands, which have been described as being another Kenya on a smaller scale.

Many people still remain to be brought under the influence of the Administration. A five-year programme has been established to bring government control to the whole Territory. With the introduction of law and order, so must the development of health bring a plan for disease-prevention, to stop the entry, particularly, of those introduced diseases that in the past have decimated much of the population. As an example of a wet tropical country the Territory has a limited tropical disease pattern. The pestilential diseases smallpox, cholera and plague, so close to our borders, are not present, and whilst there is some history of smallpox having swept the country before the coming of the European, this disease has not been seen during the rule by the United Kingdom, Australia or Germany, or during the war. During the current year 100,000 calf lymph vaccinations have been carried out.

The most important disease is malaria. Those who served as hygienists and malaria control officers during the war will realize the magnitude of the problem in peace time. For the proper economic development of the Territory malaria must be controlled, and to this end the Administration is establishing research to bring this control about, within its financial resources. For success, education must cause the people to desire it—their cooperation is essential. In the highlands of New Guinea *Cinchona* spp. culture was established before the war; then with the cutting off of 90% of the world's supply of cinchona, great impetus was given to the expansion of this culture. It must now be further expanded, and it is hoped that this extension will enable the Territory to produce the whole of its requirements of "Totaquine" and that current research will allow the establishment of village industries providing a suitable suppressive. Education will be used to stimulate village mosquito control. At present detailed research is being undertaken in the central highlands, which encourages the people to adopt a drainage system to eradicate *Anopheles farauti* from the Pit Pit swamps, and which will, in turn, make literally thousands of acres of rich fertile land available to crop culture.

Probably the next disease of significance is the disease brought in within the last century—tuberculosis. This has proven a veritable white plague in those areas of longest European habitation. An article by E. A. North and D. Jamieson in THE MEDICAL JOURNAL OF AUSTRALIA of November 25, 1950, drew significant attention to this. Physical disabilities prevent the treatment and segregation of most of the sufferers. Thus a policy was adopted of mass immunization with *Bacillus Calmette-Guérin* (B.C.G.) This programme is proceeding at present at the rate of 300,000 vaccinations *per annum*. It was commenced in the non-immune central highlands, recently explored for the first time, where were found some hundreds of thousands of people who were *Mycobacterium tuberculosis* sterile. This phase in the highlands is now nearly completed, and the vaccination team has been transferred to the hyperendemic coastal areas. The use of B.C.G. in the Territory with such a limited transport system is not without its drama, owing to the short life of the vaccine. The Commonwealth Serum Laboratories place the vaccine in their own refrigerator at an airlines office at Essendon Airport, Melbourne, on Friday afternoon. This is flown on the Saturday morning to Sydney, where it is transferred to a "Skymaster" which brings it to the Territory, arriving at Port Moresby at daylight on Sunday. From here it is transferred to Lae, Rabaul or Madang on the same day on an internal airline route. From these major centres charter aircraft fly it to its eventual destination and if necessary air-drop it to the parties in the field by no later than the Tuesday following its day of dispatch from Melbourne.

Research into treatment with streptomycin and PAS, if one remembers our limited ability to provide hospital treatment, at this stage has been most encouraging—that is, for our type of tuberculosis and our conditions. A team from the South Pacific Commission undertook research into the field diagnosis of tuberculosis in this Territory and has given much valuable information. Our own research into the most efficacious method of using B.C.G. amongst the primitive people has brought to light many facts which are now being collated for publication. It is proposed to establish in the Trobriand Islands, but on a larger scale, a replica of Aronson's classic work.

The high infant mortality rate, which reaches 500 in some areas, is receiving our attention. A branch of the Department is established to bring increasing infant and maternal welfare, and as accommodation and staff become available this work is being extended into the more primitive areas. Under the direction of Dr. F. W. Clements, now Director of Nutrition of the World Health Organization at Geneva, a nutrition survey was undertaken in the Territory in 1947. The report of the survey recently printed has caused the formation, with the widest representation, of a nutrition council in the Territory.

The antibiotic drugs, including terramycin, are being used to establish the most economic method in the treatment of such conditions as yaws, *granuloma venereum*, tropical ulcers, and those other conditions which in the past have required expensive lengthy periods in hospital. Medical surveys have been undertaken amongst the peoples of the more isolated island groups with a view to their medical rehabilitation through community development. Particular attention was given to the western islands, where depopulation caused R. W. Cilento's monographs, "The Causes of the Depopulation of the Western Islands of the Territory of New Guinea".

The increased staffing of the Department has brought to notice a cancer pattern not dissimilar from that seen amongst our own communities. It has been necessary to transfer patients to the Brisbane General Hospital for radium and deep X-ray therapy, but through the kind offices of the Commonwealth X-ray and Radium Laboratories, radium is now available within the Territory, and deep, medium and superficial X-ray therapy apparatus is on order from England.

The maximum fight against disease amongst the native population must take place in the village. To this end selected natives are being trained to give first aid in the common disease pattern and to bring improved village sani-

tation, particularly mosquito control and the disposal of wastes. This part of the programme requires great supervision, necessitating constant patrolling by our European officers, who must travel by foot, by canoe, by launch or by aircraft. A basic principle of the Department's policy is to use more and more trained native people in the Department. To this end the establishment has been approved of a central medical school along the lines of the famous Suva school. It is necessary that initial teaching will start on a lower plane than now occurs at Suva, because of the lag in education in the people of Papua and New Guinea. This lag has made their success at Suva a difficulty, though the first assistant medical practitioner should graduate from Suva at the end of this year. He is one of six who were specially selected and sent to Suva in January, 1947. It is essential that the native women accept the responsibility of nursing. The central medical school will assist to arrange this. The control of this extension in training will be the responsibility of an assistant director of the Department. It is hoped eventually to assist in the staffing of our laboratories and X-ray departments with trained native people. A commencement has been made to train natives to give dental first aid in the villages.

There is much development and survey taking place in the Territory for its future benefit. This has caused the outstripping of accommodation. This territory, so mutilated by the war, has actually had to build from the beginning again, but this has not prevented such enterprises as the wide search for oil, the planting of new crops, the rehabilitation and harvesting of plantations, an extension of commercial and trading activities and the formation of native cooperatives. All this has brought a continually increasing European population to dwell semi-permanently in the Territory. It has become the accepted policy that all necessary medical aid should be given to these people, rather than that their transfer to Australia should be required except for the most special treatments. This requires an increased staff of specialist and medical officers, but for some time to come it will require certain attributes in these officers, because it is a hard country, devoid of many amenities today. Its medical officers must be prepared to patrol widely and to put up with certain inconvenience in accommodation, and they must have a zeal and a patience to make the service a success.

The immediate problems in the Territory require a staff of 316 officers, and proposals have been made to increase this eventually to 600. A major part of this latter increase, it is hoped, will be taken by educated native people entering a fourth division of the public service. As well as 316 Europeans, over 2000 natives are now employed as hospital orderlies and as medical assistants in their villages, or are in training for these duties.

Whilst disease prevention cannot be properly divorced from disease treatment, an increased emphasis is made to all officers on the supreme importance of prevention. To this end it is required that medical officers undertake their course for the diploma of tropical medicine and hygiene at the expense of the Administration before promotion. As conditions allow, it is hoped to establish special refresher courses to meet the special problems of the Territory. An extensive lending library of text-books and journals is maintained in order that all officers may continue their studies.

It must be repeated that service conditions will not be easy for some time to come. But the Administration is determined that the policy of the Government of the Commonwealth of Australia will be made to succeed and that as quickly as possible.

J. T. GUNTHER, M.B., D.T.M. and H.,
Director of Public Health,
Papua and New Guinea.

Medical Societies.

MELBOURNE PÆDIATRIC SOCIETY.

A MEETING of the Melbourne Pædiatric Society was held on September 13, 1950, at the Children's Hospital, Carlton, Melbourne.

Tuberculous Meningitis.

DR. STANLEY WILLIAMS and DR. B. W. NEAL presented a paper entitled "Meningeal Tuberculosis in Children: A Review of Forty Patients" (see page 676).

DR. A. W. WILLIAMS read a paper entitled "Pathology of Tuberculous Meningitis, with Particular Reference to Modification in Pathology following Treatment with Streptomycin" (see page 680).

DR. REGINALD WEBSTER said that he would discuss the manner in which tubercle bacilli were deposited in the meninges in numbers sufficient to evoke the exudative inflammatory reaction characteristic of tuberculous meningitis. For many years the pathogenesis of tuberculous meningitis seemed to present no problem, it being generally agreed that it was the result of direct meningeal infection by way of the blood-stream, and appeared as a phase of miliary tuberculosis. That belief was based on the frequent coincidence of tuberculous meningitis and miliary tuberculosis, especially in infants; but it had been challenged, and apparently successfully, by Rich and McCordock (1933), who maintained that tuberculous meningitis arose independently of miliary tuberculosis and was to be attributed to infection of the meninges by the discharge of the contents of a contiguous caseous focus into the subarachnoid space. The views advanced by Rich and McCordock gained general, though not unqualified, support from an investigation of the question by MacGregor and Green (1937), and in 1944 James McMurray published in the *Archives of Disease in Childhood* observations gained from a study of the brains and general autopsy features of 11 children who had died of tuberculous meningitis. From his findings McMurray concluded that tuberculous meningitis commonly ensued on the extension into the subarachnoid space of a focus in adjacent tissues, such as the meninges, the cerebral cortex or the cranial bones, the *tegmen tympani* and mastoid process particularly. A review of any adequate series of carefully performed autopsies would show (i) that there might be no meningitis in the presence of miliary tuberculosis of even maximum intensity, and conversely (ii) that meningitis occurred not infrequently in the absence of miliary tuberculosis.

Dr. Webster went on to say that in 1947 he had examined the clinical records of 95 children from whom he had recovered *Mycobacterium tuberculosis* by bacteriological investigation of the gastric content. Among those 95 children of the pre-streptomycin era there were 20 who had died from tuberculous meningitis. The usual finding at autopsy was that the pulmonary lesion of the primary complex, more often than not overshadowed by the complementary tuberculous changes in the tracheo-bronchial lymph nodes, was the precursor of a variable degree of miliary sowing in the lungs and other viscera. In three children of that group, however, tuberculous meningitis and the primary complex to which it was indirectly referable were unaccompanied by any macroscopically detectable miliary sowing in the thoracic or abdominal viscera. In a particular instance provided by a little girl, aged three and a half years, who had died of tuberculous meningitis and whose gastric content yielded a culture of *Mycobacterium tuberculosis*, the only manifestations of tuberculous disease other than the meningitis to be discovered in the body by gross inspection were an apparently soundly healed Ghon focus and dry calcareo-caseous changes in the tracheo-bronchial lymph nodes. Yet that child was eliminating tubercle bacilli, intercepted in the laboratory in the gastric content, and the observation not only provided an example of the occurrence of tuberculous meningitis apart from miliary tuberculosis, but indicated also that the determination of healing in a primary complex might be a matter of very great difficulty. Rich and McCordock had found that the injection of massive doses of virulent tubercle bacilli into the blood-stream of experimental animals regularly caused generalized miliary tuberculosis but did not induce simultaneous acute exudative meningitis. The immediate result, as it affected the meninges, of experimental infection by way of the blood-stream, was the production of sparsely distributed discrete tubercles; the exudative inflammatory reaction of tuberculous meningitis, when it did occur, did not supervene for the several weeks required for the caseation, softening and discharge of the contents of one or more of the foci into the subarachnoid space. On the other hand, when tubercle bacilli were introduced directly into the subarachnoid space by way of the optic foramen, the diffuse inflammatory reaction characteristic of tuberculous meningitis followed immediately.

Dr. Webster then asked if tuberculous meningitis was not to be regarded as a phase of miliary tuberculosis, how the undoubtedly frequent coincidence of miliary tuberculosis and tuberculous meningitis in children, and in infants especially, was to be explained. Infants and very young children had little opportunity to acquire resistance to tuberculous infec-